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RESEARCH ARTICLE

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Synthesis and applications of 3,4-dihydroxy-2,5-bis- (2'-(4'-substituted-oxazolinyl)) furan

Abstract Three 3,4-dihydroxy-2,5-bis-(2'-(4'-substituted-oxazolinyl)) furans were synthesized at 90%–94% yields from reaction of 3,4-dihydroxyfuran-2,5-dicar-boxylic acid or its dimethyl ester with chiral *β*-amino alcohol *via* a one-step process. Their chemical structures were determined by ^{1}H NMR, IR, MS, and elemental analysis. With these chiral bisoxazoline ligands, the asymmetric reductive reaction of *β*-acetonaphthalene with KBH_4 or $NaBH_4$ was preliminarily studied. The enantiomeric excess of the reduction product was up to 83.2% with cyclohexane as the solvent, the molar ratio of ligand: reductive agent: *β*-acetonaphthalene is 0.04:1.6:1, and 72-hours reaction time at 0℃. Furan-containing bisoxazoline with 4-benzyl on oxazoline rings exhibited higher enatioselectivity than congeneric bisoxazolines with 4-ethyl on oxazoline rings.

Keywords 3,4-dihydroxy-2,5-bis(2'-(4'-substituted-oxazolinyl)) furan, bis(oxazoline), chiral reagent, asymmetric reduction, synthesis

1 Introduction

Since Butula et. al. prepared the first optically active bis(oxazoline) in 1976, the synthesis and applications of bis(oxazoline)s have been rapidly developed [1]. Undoubtedly, this research area has become one of the most active in organic synthesis. Chiral bis(oxazoline) ligands have widespread uses because they hold special structural characters and provide high enantioselectivity in a variety of asymmetric catalytic reactions [2–6]. 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 [2–13]: (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 poly(*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.

In the present study, 3,4-dihydroxyfuran-2,5-dicarboxylic acid or its dimethyl ester reacted with chiral 2-amino-1-butanol or L-phenylalaninol under reflux through water deprivation or alcohol deprivation within 18–23 h, to obtain the title compounds (**1** and **2**) as novel chiral bis(oxazoline) ligands (scheme 1). The above method afforded high yields and simple workup procedure. At the same time, the enatioselectivity of the asymmetric reductive reaction of *β*-acetonaphthalene with KBH_4 or $NaBH_4$ as reducing agent was preliminarily investigated with compound **1** and **2** (see Eq.(1)).

2 Experimental

Melting points were determined by the capillary method and uncorrected. ^{1}H NMR spectra were measured on a Varian UNITY INOVI-500 NMR spectrometer at 500 MHz, using CD_3OD as solvent and TMS as internal standard. Infrared spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. Mass spectra were taken on a LCQ DECA XP LC/MS system. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer. Optical rotation values were measured at 20℃ on a POLARTRONIC HNQW

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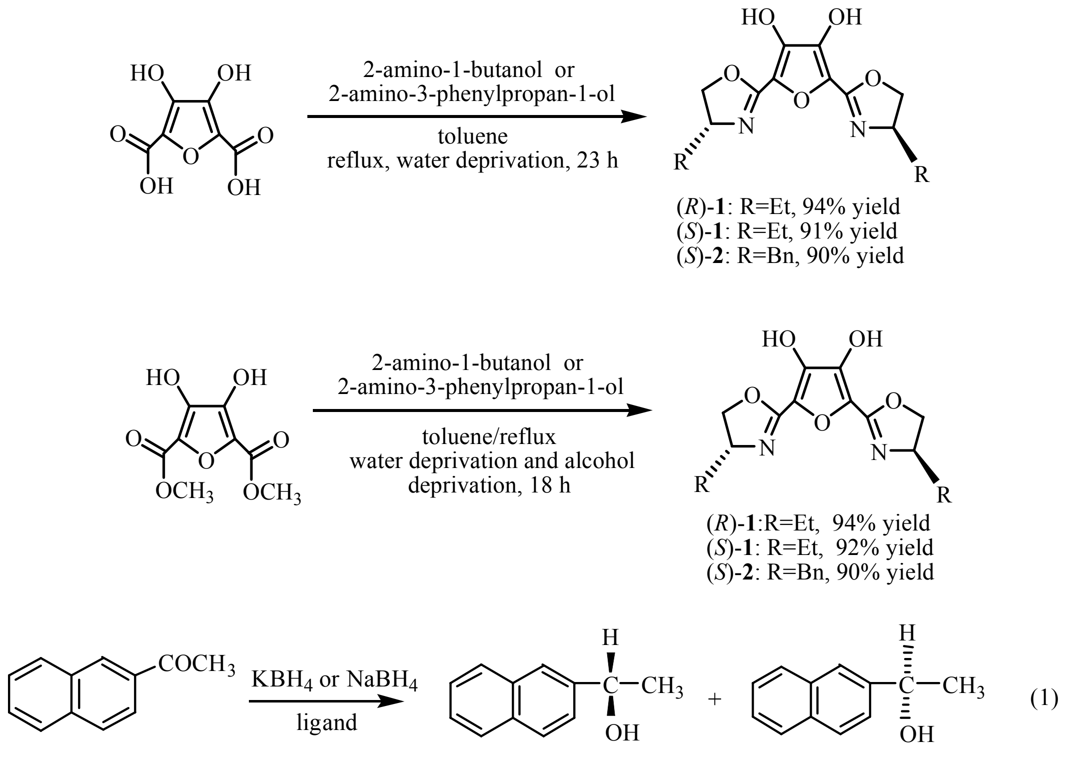

Scheme 1

5 polarimeter with a 10-cm cell. 2-Amino-1-butanol was purchased from Fluka Chemical Co.. 3,4-Dihydroxyfuran-2,5-dicarboxylic acid and its dimethyl ester were prepared as described in the literature [14], and L-phenylalaninol was obtained according to the literature [15]. The other reagents were analytically pure.

2.1 Preparation of 3,4-dihydroxy-2,5-bis(2'-(4'-substituted-oxazolinyl))furan (**1** and **2**)

General procedure A A mixture of 3,4-dihydroxy-furan-2,5-dicarboxylic acid (0.75 g, 4 mmol), chiral amino alcohol (8 mmol) and toluene (40 mL) was refluxed and dehydrated for 23 h. Toluene was then removed under reduced pressure. After cooling to ambient temperature, the residue was purified by silica gel column chromatography (0.149–0.074 mm particle diameter silica gel) with ethanol as the eluent to produce the title compound.

General procedure B A mixture of dimethyl 3,4-di-hydroxyfuran-2,5-dicarboxylate (0.87 g, 4 mmol), chiral amino alcohol (8.04 mmol) and toluene (40 mL) was heated under reflux for 18 h to deprive alcohol and water The solvent was then removed under reduced pressure. After cooling to room temperature, the residue was purified by column chromatography on 0.149–0.074mm particle diameter silica gel with ethanol as the eluent to yield the title compound.

2.2 Effects of 3,4-dihydroxy-2,5-bis(2'-(4'-substituted-oxazolinyl)) furan on the enantioselective KBH_4-or $NaBH_4$-catalyzed reductive reaction of β-acetonaphthalene

A mixture of KBH_4 (0.51 g, 9.6 mmol), 3,4-dihydroxy-2,5-bis[2'-(4'-ethyloxazolinyl)]furan (0.24mmol) and cyclohexane (10 mL) was stirred for 1 h at ambient temperature under the protection of nitrogen, then β-acetonaphthalene (1.02 g, 6.0 mmol) was stirred in. After the addition, the reaction mixture was stirred for 72 h below 0℃. The resulting mixture was then acidified with dilute hydrochloric acid and the organic layer was separated. The aqueous layer was extracted with diethyl ether, dichloromethane, and the organic layers were combined and dried with anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel with 0.149–0.074 mm particle diameter, using CH_2Cl_2 as the eluent to produce white solid compound. The configuration of the product was determined by optical rotation and enantiomeric excess was determined by a comparison of specific rotation of the product of ethanol solution (0.05 g/mL) with that of optically pure (+)-1-(naphthalene-2-yl)ethanol [$[\alpha]_D^{20}$= +38 (c=5, C_2H_5OH)] or (-)-1-(naphthalene-2-yl)ethanol [$[\alpha]_D^{20}$= -40 (c=5, C_2H_5OH)] [16]. The experimental results were shown as Table 1.

Table 1 Effect of different ligands on enantioselective KBH_4- or $NaBH_4$-catalyzed reductive reaction of β-acetonaphthalene

Ligand	n(L) : n(R) : n(S)^a	Solvent	Reaction time/ h	t ℃	Yield/ %	ee^b/ %	Absolute configuration
—	0:1.6:1	Cyclohexane	60	r. t.	42.0	—	—
(+)-2-amino-1-butanol	0.04:1.6:1	Cyclohexane	60	r. t.	65.4	10.2	R
(+)-2-amino-1-butanol	0.04:1.6:1	CH_3OH	60	r. t.	76.3	7.0	R
(-)-2-amino-1-butanol	0.04:1.6:1	Cyclohexane	60	r. t.	62.6	9.1	S
(*R*)-**1**	0.04:1.6:1	$PhCH_3$	60	r. t.	61.2	57.3	R
(*R*)-**1**	0.04:1.6:1	CCl_4	60	r. t.	68.8	56.4	R
(*R*)-**1**	0.04:1.6:1	CH_2Cl_2	60	r. t.	65.1	62.5	R
(*R*)-**1**	0.04:1.6:1	C_2H_5OH	60	r. t.	84.5	45.4	R
(*R*)-**1**	0.04:1.6:1	CH_3OH	60	r. t.	86.7	40.3	R
(*R*)-**1**	0.04:2.0:1	CH_3OH	60	r. t.	87.0	42.1	R
(*R*)-**1**	0.04:1.6:1	Cyclohexane	60	r. t.	73.4	65.8	R
(*R*)-**1**	0.04:1.6:1	Cyclohexane	48	r. t.	61.8	52.1	R
(*R*)-**1**	0.04:1.6:1	Cyclohexane	72	r. t.	85.4	75.2	R
(*R*)-**1**	0.04:1.6:1	Cyclohexane	72	0	75.8	80.6	R
(*R*)-**1**	0.04:1.6:1	Cyclohexane	72	50	98.4	49.5	R
(*R*)-**1**	0.04:1.0:1	Cyclohexane	72	r. t.	60.5	60.4	R
(*R*)-**1**	0.04:2.0:1	Cyclohexane	72	r. t.	86.2	76.0	R
(*R*)-**1**	0.02:1.6:1	Cyclohexane	72	r. t.	66.7	59.6	R
(*R*)-**1**	0.01:1.6:1	Cyclohexane	72	r. t.	58.3	50.5	R
(*R*)-**1**	0.04:1.6:1^c	Cyclohexane	72	r. t.	83.6	74.1	R
(*S*)-**1**	0.04:1.6:1	Cyclohexane	72	0	77.9	78.8	S
(*S*)-**2**	0.04:1.6:1	Cyclohexane	72	0	71.4	83.2	S

a. L, R, S represent chiral ligand, reducing agent, which is KBH_4 unless noted otherwise, and acetonaphthalene, respectively. b. ee represents enantiomeric excess. c. Its reducing agent is $NaBH_4$.

3 Results and discussion

3.1 Characteristic of products

*3.1.1 (R)-(-)-3,4-dihydroxy-2,5-bis(2'-(4'-ethyloxazolinyl))-furan ((R)-**1**)*

Following either general procedure A or procedure B, a colorless sticky liquid (*R*)-**1** was obtained at 94% yield. $[\alpha]_D^{20}$= -10 (c= 0.5, C_2H_5OH). Elemental analysis calcd (%) for $C_{14}H_{18}N_2O_5$: C 57.13, H 6.16, N 9.52; found: C 57.32, H 6.38, N 9.40. ^1H NMR (CD_3OD), δ: 1.03 (t, J=7.5 Hz, 6H, CH_3), 1.62-1.73 (m, 4H, CH_2CH_3), 3.10-3.15 (m, 2H, NCH), 3.57 (dd, J=7.0 Hz, 11.5 Hz, 2H, OCH_2), 3.77 (dd, J=3.5 Hz, 11.5 Hz, 2H, OCH_2), 4.55 (s, 2H, OH). IR (KBr), v/ cm^{-1}： 3276 (OH), 2968, 2941, 2880 (C-H), 1652 (C=N), 1518 (Furan C-C), 1055 (C-O). ESI-MS, *m/z* (%)： 317($[M+Na]^+$, 100).

*3.1.2 (S)-(+)-3,4-dihydroxy-2,5-bis(2'-(4'-ethyloxazolinyl))-furan ((S)-**1**)*

This compound was synthesized as colorless sticky liquid at 91% yield according to general procedure A, and 92% yield following general procedure B. $[\alpha]_D^{20}$=+10 (c=0.5, C_2H_5OH). ^1H NMR spectrum of the compound (*S*)-**1** is the same as that of the compound (*R*)-**1**.

*3.1.3 (S)-(+)-3,4-dihydroxy-2,5-bis(2'-(4'-benzyloxazolinyl))-furan ((S)-**2**)*

This compound was obtained as white solid at 90% yield according to general procedure A, and 90% yield following general procedure B. mp162.0-163.5℃. $[\alpha]_D^{20}$= +18 (c =1.0, CH_3OH). Elemental analysis calcd (%) for $C_{24}H_{22}N_2O_5$: C 68.89, H 5.30, N 6.69; found: C 68.51, H 5.43, N 6.86. ^1H NMR (CD_3OD), δ: 2.79 (dd, J=7.0 Hz, 14.0 Hz, 2H, CH_2Ph), 2.88 (dd, J=7.0 Hz, 13.5 Hz, 2H, CH_2Ph), 3.26-3.31 (m, 2H, NCH), 3.46 (dd, J=6.5 Hz, 11.0 Hz, 2H, OCH_2), 3.62 (dd, J=4.0 Hz, 11.0 Hz, 2H, OCH_2), 7.23-7.34 (m, 10H, ArH). Among the protons described above, two active hydrogens of OH were substituted by deuterium. IR (KBr), v/cm^{-1}： 3344 (OH), 3034 (Ar C-H), 2935 (C-H), 1605 (C=N), 1496 (Furan or Ar C-C), 1454, 1378, 1322 (CH_2), 1057 (C-O). ESI-MS, *m/z* (%)： 419 ($[M+H]^+$, 100).

3.2 Effect of various conditions on the reductive reaction of *β*-acetonaphthalene

The enantioselectivity of 3,4-dihydroxy-2,5-bis(2'-(4'-substitutedoxazolinyl))furan **1** and **2** in asymmetric reductive reaction was investigated using *β*-aceto-naphthalene as substrate and KBH_4 or $NaBH_4$ as reducing agent. The experimental results were shown in Table 1.

As indicated from the data in Table 1, compounds **1** and **2** exhibited good enantioselectivity in reductive reaction of *β*–acetonaphthalene. Because the enantioselectivity was determined only by the chirality of oxazoline ring derived from chiral amino alcohol, so the absolute configuration of the reductive product was in agreement with that of the corresponding chiral amino alcohol. The results indicated that many factors made impact on enantiomeric excess of the reductive product, including solvents, reaction time, reaction temperature, structure and amount of ligands, reducing agents and their amount etc. Among them, solvents, reducing agents and their amounts had less effect on the enantiomeric excess of the reductive product.

Cyclohexane was suitable for the use as solvent. Reductive activity of KBH_4 was similar to that of $NaBH_4$, and the suitable amount of reducing agent was as high as 1.6 times that of substrate. However, reaction time, reaction temperature, the amount of ligands had a great effect on enantiomeric excess of the reductive product. At room temperature, the enantiomeric excess increased because of the lengthy reaction time. When the reaction temperature was raised, the yield of the product increased, but its enantiomeric excess decreased. Both record an increase when the amount of ligand was raised.

In conclusion, the asymmetric reduction gave the product in 75.8% with enantiomeric excess up to 80.6% with cyclohexane as the solvent, the molar ratio of ligand: reductive agent: *β*-acetonaphthalene =0.04:1.6:1, and 72 h reaction time at 0℃. The results exhibited that the furan-containing bis(oxazoline) held good rigid C_2-symmetric chirality-inducing unit that led to good enantioselectivity.

Table 1 showed that the enantioselectivity of (*S*)-**2** in the reductive reaction of *β*-acetonaphthalene was up to enantiometric excess 83.2% exceeding that of (*R*)-**1** or (*S*)-**1**, and the furan-containing bisoxazoline with 4-benzyl on oxazoline rings exhibited higher enantioselectivity than the congeneric bisoxazolines with 4-ethyl on oxazoline rings.

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