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C_2 Symmetric Synthesis of *Bis*(amino alcohol)oxalamides and Its Catalytic Activity

ADNAN ÇETIN
Department of Science, Faculty of Education, Mus Alparslan University, Mus, Turkey
Fax: (90)(436)2120853; Tel: (90)(436)2127459; E-mail: adescan21@gmail.com

The aim of this study is to evaluate C_2 symmetric synthesis of *bis*(amino alcohol)oxalamides and the catalytic activity diethyl zinc to benzaldehyde. Syntheses of diamidediols were achieved nearly quantitatively by reacting oxalic acids methyl esters with amino alcohols directly in a single step reactions and mild conditions. Four modular and rigid diamidediols having C_2-symmetry were synthesized forming oxalic moiety main core. The catalytic effects of the N,N'-*bis*[(1R)-1-ethyl-2-hydroxyethyl]ethanediamide, N,N'-*bis*[(1S)-1-benzyl-2-hydroxyethyl]-ethanediamide, N,N'-*bis*[(1S)-1-isobutyl-2-hydroxyethyl]ethanediamide and N,N'-*bis*[(1S)-1-secbutyl-2-hydroxyethyl]ethanediamide were tested and also N,N'-*bis*[(1S)-1-benzyl-2-hydroxyethyl]ethanediamide, N,N'-*bis*[(1S)-1-isobutyl-2-hydroxyethyl]ethanediamide were synthesized. The catalytic activity of C_2-symmetric diamidediols on the addition reaction of diethyl zinc to benzaldehyde and effects of alkyl moiety bonded to stereogenic center on enantioselectivity were conducted out.

Key Words: Enantioselectivity, Oxalamide, Catalytic, Diethyl zinc.

INTRODUCTION

The synthesis off new chiral ligands to use as catalyst in synthetic organic chemistry area are quite concerned[1-4]. A variety of the reactions have found application as efficient promotors for the addition of diethyl zinc to prochiral aldehydes[5]. Since the chiral secondary alcohols are integral parts of biological active compounds and versatile intermediates for further transformation[6,7]. Several examples are cited in literature for the production of enantiomers with high stereoselectivity using chiral catalysts or ligands derived from the starting chiral materials. Several kind of compounds that are enantiopure prepared carefully by control synthetic strategies and racemic at certain conditions[8,9]. The C_2-symmetric ligands which were used are Taddols[10], Binols[11], diamine, *bis*sulfonamides[12], *bis*oxalins[13]. Oxalic or malonic acid *i.e.*, multidentate ligands prepare at the C_2-symmetric was one of the good starting materials[14]. These's carboxyl moieties with a lot chiral compounds to interact becomes too functional C_2-symmetric chiral ligands[15]. In that study oxalic acid's methyl ester by using one step and quantitative yield rigid and C_2-symmetric compound, *i.e.*, chiral *bis*(amino alcohol)oxalamides (diamidediols) was prepared and tested

in the catalytic activity effects in the addition of diethyl zinc to benzaldehyde. These studying oxazolines[1], styrene[16], sülfonimine[17], organocatalyst[18], ketone aldols[19], cyclic[20], alkynes[21,22], acyclic amino alcohols[23,24], N-aryl α-amino ketones[25], 1-naphthyl[26,27], disülfinides[28,29], diselenides[30]. Using as catalyst diamidediols in the addition of enantioselectivity of diethyl zinc to aldehydes first time had been achieved by Pedro *et al.*[31]. Pedro *et al.*[31] prepared oxalic chloride and malonic chloride before amino acid with esters to affect after than development of ester with $LiBH_4$ reduce copy of C_2-symmetric one serial chiral *bis*(amino alcohol)oxalamides (diamidediols). Reaction (S)-alcohols gives titanium (IV) isopropoxide when Ti(IV) isopropoxid didn't use contrast configuration (R)-alcohols gave. But conversion available more or less, furthermore, it was retained the presence of bulky groups at the carbons which links with OH moiety has to induce enantioselectivity. But this synthesis occurs in two ways and especially yield of the reaction has reduced *ca.* 55 %. In this study, we have synthesized four new high yield C_2-symmetric diamidediols, rigid and chiral ligands which mild forming oxalyl main core.

EXPERIMENTAL

All chemicals were reagent grade unless otherwise specified. Melting points were determined with a GALLENKAMP Model apparatus with open capillaries and are uncorrected. Infrared spectra were recorded on a MATTSON Model 1000 spectrophotometer. The elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 high performance digital FT-NMR spectrometer, with tetramethylsilane as the internal standard for solutions in $CDCl_3$. *J* values are given in Hertz. Optical rotations were recorded using an Perkin-Elmer Model 341 polarimeter. GC Chromatography was Hewlett-Peckett HP 6890 Series GC system.

Synthesis of dimethyloxalate (DMO) (1): Methanol (38.4 g, 1.2 mol) was added drop-wise to pyridine (47.4 g, 0.6 mol). A solution of oxalyl chloride (38 g, 0.3 mol) in benzene (250 mL) was added to the mixture in 3 h under dry N_2 atmosphere at room temperature. The mixture was then refluxed for 3 h and kept at room temperature for 1 day. The solvent was evaporated under reduced pressure. The white solid compound was extracted with cold ethers and dried over Na_2SO_4. The product was recrystallized from ether to yield 32 g (92 %), m.p. 54-54.5 ºC. m.w. 118 g (required C, 40.68; H, 5.09; found: C, 40.62; H, 5.11). ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (6H, s).

Synthesis of N,N'-*bis*[(1R)-1-ethyl-2-hydroxyethyl]ethanediamide (2): A solution of (R)-2-amino-1-butanol (2.76 g, 31 mmol) in methanol (10.0 mL) was added drop wise to a solution of dimethyl oxalate (1.83 g, 15.5 mmol) in methanol (30.0 mL) at room temperature for 0.5 h. After addition, solid product was precipitated and then filtered and washed with ether to give 7.1 g (99 %) of white compound **2**. m.p: 210-212 ºC; $[\alpha]_D^{25}$ + 25.3 (c, 1.0 DMSO); IR (KBr, ν_{max}, cm^{-1}): 3365, 3280, 2967, 2935, 2854, 1665, 1530, 1048; ^1H NMR (400 MHz, DMSO-d_6): δ 0.85 (6H,

t, *J* = 7.4 Hz), 1.42 (2H, m), 1.55 (2H, m), 3.3 (4H, m), 3.7 (2H, m), 4.7 (2H, brs), 8.2 (2H, d, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4, 24.4, 54.2, 63.7, 161.7.

Synthesis of N,N'-*bis*[(1S)-1-benzyl-2-hydroxyethyl]ethanediamide (3): Following an analogous procedure that has been described for **2**, from L-phenylalanilol (4.75 g, 31.5 mmol) were obtained almost quantitative (5.56 g, 99 %) **3**. m.p. 252-253 ºC; $[\alpha]_D^{25}$ - 43.8 (c 0.03, MeOH), IR (KBr, ν_{max}, cm^{-1}): 3416, 3300, 3063, 3037, 3247,1658, 1523, 1047; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.77 (2H, dd, *J* = 13.5, *J* = n5.4 Hz), 2.91 (2H, dd, 13.5, 5.4 Hz), 3.43 (4H, m), 3.95 (2H, m), 4.93 (2H, t, *J* = 5.6 Hz), 7.3-7.1 (10 H, m), 8.4 (2H, d, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.6, 53.4, 62.7, 126.4, 128.6, 129.4, 139.3, 159.9.

Synthesis of N,N'-*bis*[(1S)-1-isobutyl-2-hydroxyethyl]ethanediamide (4): Following an analogous procedure that has been described for **2**, from L-izoleucin (3.744 g, 0.032 mmol) were obtained almost quantitative (9.2 g, 99 %) (**4**) m.p. 174-176 ºC; $[\alpha]_D^{25}$ = -30.1 (c 1.0 MeOH); IR (KBr, ν_{max}, cm^{-1}): 3353, 3288, 2960, 2935, 1657, 1535, 1099; ^{1}H NMR (DMSO-d_6): δ 0.88 (6H, d, *J* = 6.4 Hz), 0.90 (6H, d, *J* = 6.4 Hz), 1.3 (2H, m), 1.45 (4H, m), 3.4 (4H, m), 3.85 (2H, m), 4.81 (2H, t, *J* = 5.6 Hz), 8.3 (2H, d, *J* = 9.3); ^{13}C NMR (DMSO-d_6): δ 22.3 (q), 23.6 (q), 24.8 (d), 40.0 (t), 50.1 (d), 63.8 (t), 160.2 (s).

Synthesis of N,N'-*bis*[(1S)-1-sec-butyl-2-hydroxyethyl]ethanediamide (5): Following an analogous procedure that has been described for **2**, from L-leusinol (4.07 g, 0.034 mmol) were obtained almost quantitative (10 g, 99 %) (**5**) m.p. 190-192 ºC, $[\alpha]_D^{39}$ = + 25.2; (c, 1.0 DMSO); IR (KBr, ν_{max}, cm^{-1}): 3435, 3288, 2967, 2935, 2877, 1651, 1529, 1080; ^{1}H NMR (DMSO-d_6): δ 0.90 (6H, t, *J* = 6.5 Hz), 0.95 (6H, d, *J* = 6.4 Hz), 1.38 (2H, m), 1.4 (2H, dd, *J* = 8.6, *J* = 4.4 Hz), 1.65 (2H, dd; *J* = 8.6, *J* = 4.4 Hz), 3.5 (4H, m), 3.8 (2H, m), 8.2 (2H, d, *J* = 9.2 Hz); ^{13}C NMR (DMSO-d_6): δ 11.6 (q), 15.9 (q), 25.5 (d), 35.4 (t), 56.0 (t) 61.3 (d), 160.3 (s).

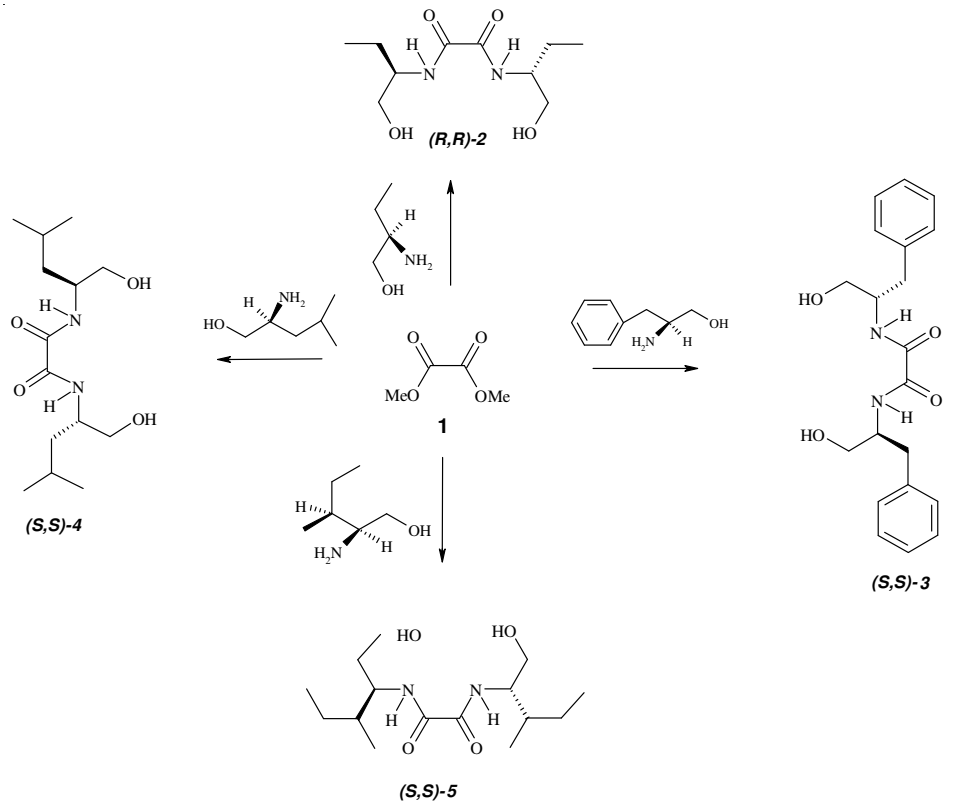
Aldehydes enantioselectivity diethyl zinc in the addition optimum conditions: It was optimized the optimum conditions of aldehydes enantioselectivity diethyl zinc, time, keep warm, ligand concentrations Ti(OiPr)$_4$ concentrations. As a result of this investigation; for transformation optimum conditions: time: 24 h; temperature: 0 ºC; ligand concentration: 0.04 mmol/mL; Ti(OiPr)$_4$ concentration: 3.3 mmol/mL.

General procedure in the addition of diethyl zinc to benzaldehyde enantioselectivity: Dissolve the ligand in dichloromethane (0.2 mmol, 5 mL) in the argon atmosphere. After 1 h the solution was cooled at 0 ºC, diethyl zinc solution (3 mL, 3 mmol) was added in the hexane (1 M). After 0.5 h benzaldehyde (1 mmol) was added and left for 24 h. After than reaction mixture (1 M, 20 mL HCl) was ended and filtered, ether (3 × 15 mL) was extracted. Organic phase was dried by without water $MgSO_4$, filtered and the solvent was evaporated. On the silica hexane: diethyl ether (3:1) with flash chromatography was elued. With gas chromatography method by using siklodextrin column was founded enantiomeric excess.

Gas chromatography conditions: Gas chromatography model: HP6890; Colon: siklodextrin B; Colon long: 30 m; Colon's inner- diameter: 0.25 mm; Syringe heat: 200 ºC; Detector heat: 200 ºC; First heat: 110 ºC; Last heat: 200 ºC ramp/min; First and last heat waits: 10 min; Flow fast: 0.6 mL/min; Transporter gas: He; Detention timing: Benzaldehyde: 2.85 min; (R)-1-phenyl-1-propanol: 10.6 min; (S)-1-phenyl-1-propanol: 10.7 min.

RESULTS AND DISCUSSION

The design and synthesis of new molecules able to act as chiral symmetric ligands in catalytic asymmetric reactions is one of the most important goals in modern organic chemistry[1,32,33]. Herein, we reported the synthesis of four chiral *bis*(amino alcohol)oxalamides from amino alcohols derived from natural amino acids. The chiral, rigid and C_2-symmetric macrocycles were synthesized from *bis*(amino alcohol)oxalamides (S,S)-3, (S,S)-4, (S,S)-5 and (R,R)-2 as shown in **Scheme-I**. Chiral *bis*(amino alcohol)oxalamides were synthesized from (R)-2-amino-1-butanol, (L)-leucinol, (L)-phenylalanilol and (L)-isoleucinol reacted with dimethyloxalate in methanol at room temperature, respectively. Chiral *bis*(amino alcohol)oxalamides were obtained in high yield (99 %). C_2-Symmetric four

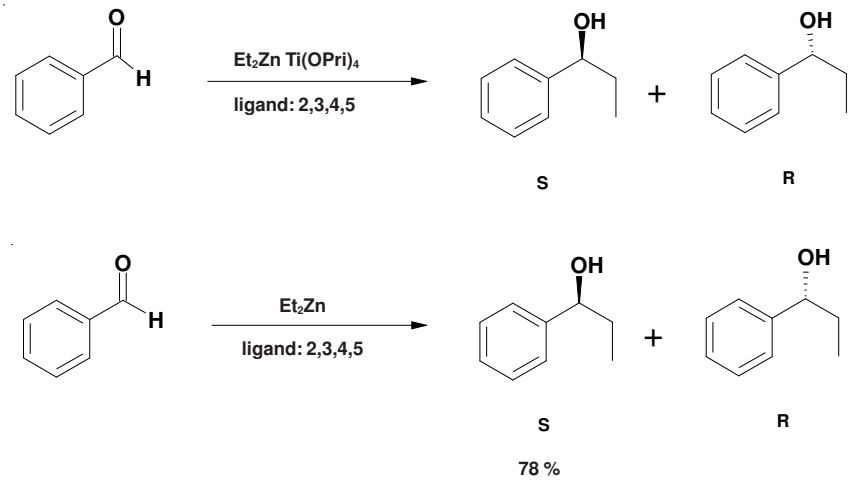


Scheme-I: Synthesis of *bis*(amino alcohol)oxalamides

bis(amino alcohol)oxalamides (diamide diols) were synthesized and characterized by spectroscopic methods (Table-1). The synthesized ligands in this study, having C_2-symmetry and complexation reactions of the C_2-symmetric compounds, were different from non-symmetric ones. It is presumed that the symmetry of the ligands might play an important role in multi-element preconcentration due to the formation of a chiral environment and the catalytic effect of the symmetric ligands to bond the metals. In this study, oxalic acid's methyl ester by using one step and quantitative yield rigid and C_2-symmetric four items chiral *bis*(amino alcohol) oxalamides (diamide diols) was prepared. The catalytic activities of C_2-symmetric diamide diols in the addition of diethyl zinc to benzaldehyde are shown in **Scheme-II**. These diamide diols chiral ligands were employed as catalyst in the asymmetric addition of diethyl zinc to benzaldehyde (Table-2). Finally, after 24 h at 0 ºC and % 10 mol ligands concentrate have ascertained the suitable conditions. Indeed the asymmetric diethyl zinc addition to aldehydes catalyzed by chiral titanium(IV) complexes is a complicated catalytic system since an excess of $Ti(OiPr)_4$ is required in order to achieve the best enantioselectivity.

TABLE-1
MELTING POINT AND YIELD OF SYNTHESES OF DIAMIDEDIOLS

Ligand	m.p. (ºC)	Yield (%)	Rotation angle
2	210-212	99	$[\alpha]_D^{39}$ = +23.5 (C1, CH_3OH)
3	252-253	99	$[\alpha]_D^{25}$ = –43.8 (C1, CH_3OH)
4	174-176	99	$[\alpha]_D^{25}$ = +24.5 (C1, CH_3OH)
5	190-192	99	$[\alpha]_D^{39}$ = +25.4 (C1, CH_3OH)



Sheme-II: Addition of diethyl zinc to benzaldehyde

TABLE-2
SOLVENT AND TEMPERATURE EFFECTS ON THE REACTION OF IN THE ADDITION OF DIETHYL ZINC TO BENZALDEHYDE AT 273 K

Ligand	Solvent	Time (h)	Yield (%)	Selectivity	ee (%)
2	Hexane	24	70	53.5	7 (*S*)
3	Hexane	24	68	55.5	11(*S*)
4	Hexane	24	70	52.5	5 (*S*)
5	Hexane	24	72	57.5	15(*S*)
2	$Ti(OiPr)_4$	24	68	63.5	27 (*R*)
3	$Ti(OiPr)_4$	24	72	67.5	35 (*R*)
4	$Ti(OiPr)_4$	24	70	59.0	18 (*R*)
5	$Ti(OiPr)_4$	24	75	60.5	21 (*R*)

Conclusion

The synthesis of four chiral *bis*(amino alcohol)oxalamides from amino alcohols derived from natural amino acids are reported. The catalytic activity of C_2-symmetric diamidediols in the addition of diethyl zinc to benzaldehyde and effects of alkyl moiety bonded to stereogenic center on enantioselectivity were conducted. In these studies a correlation obtained about enantioselectivity which on the alkyl group of chiral center. For this reason, the conversion of amino acids to amino alcohol containing tertiary OH moiety by Grignard reactions and the interaction of these amino alcohol with diamide diols, in which dialcohol acids methyl esters can contribute to occur diamide diols having tertiary OH moiety. On the other hand, it is not ascertain any correlation of alkyl moiety of the chiral center on the enantioselectivity yet. We have established that ligand **3** is higher %ee than the other ligands. In present study, the phenyl moiety has caused a significant interaction in the behaviour of the benzaldehyde. C_2-symmetric diamidediols have illustrated in depth the diversity of useful products that can be obtained through the use of these powerful versatile chiral reagents. In particular, the utility and ability of C_2-symmetric *bis*(amino alcohol)oxalamides as a catalyst in a number of asymmetric reactions have been established.

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