Res Chem Intermed
DOI 10.1007/s11164-013-1225-x

Novel approach to stereoselective synthesis of (*E*)/(*Z*)-(*N*-acyl-oxazolidinone)-eneglycinates

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Received: 19 February 2013 / Accepted: 20 April 2013

Abstract (*E*)-(*N*-Acyl-oxazolidinone)-eneglycinates were synthesized with high stereoselectivity and in good yield by condensation of aldehydes with glycinates. (*Z*)-Eneglycinates could be prepared in high purity and moderate yield by transformation of (*E*)-eneglycinates under mild conditions. The effect on the (*E*)/(*Z*)-configuration of eneglycinates of steric hindrance by α-substituents on the aldehyde was also examined. The software MMFF94 was used to explain the transformation of the thermodynamic product into the kinetic product and a plausible mechanism is given.

Keywords Eneglycinates · Stereoselectivity · Steric hindrance · Configuration

Introduction

Nitrogen-containing heterocycles, for example pyrazoles, pyrimidines, and pyrroles [1–6], are important intermediates in the synthesis of a variety of biologically active natural products and pharmaceutical drugs. (*E*)/(*Z*) substituted enamine derivatives are vital synthons for these azaheterocycles. Diverse approaches have been developed for construction of (*E*)/(*Z*) substituted enamine derivatives. Sabrina Buchini's group used commercially available propionaldehyde diethyl acetal to prepare the key intermediate (*E*)-3-dimethylamino-2-methylprop-2-enal **1** for synthesis of the target pyrimidinone [7]; Kah Toh's group synthesized substituted pyrrole derivatives via

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Published online: 31 May 2013

preparation of the intermediates (*E*)/(*Z*)-*N*-allyl/propargyl enamine carboxylates **2** [8]; Alessandro Balbi's group constructed novel pyrazole derivatives via the intermediates (*E*)-β-(dimethylamino)vinyl aldehydes **3** [9] (Fig 1). These methods suffer from such problems as harsh reaction conditions, use of toxic or expensive reagents, tedious procedures, and low yields. Hence, there is still a demand for versatile methods for synthesis of the important building blocks (*E*)/(*Z*)-substituted enamine structures from accessible starting materials, with control of the selectivity of substitution.

Herein we report preparation of new flexible (*E*)/(*Z*)-functionalized eneglycinates (**4**-**7**) (Fig. 1) by a new facile route. **4** and **5** were obtained with high (*E*)/(*Z*) selectivity and in high yield. **4** could be converted to **5** under specific conditions. These new compounds could be used as useful building blocks for a variety of biologically active natural products and pharmaceutical drugs [1–4].

Our original work focused on construction of the β-lactam ring **14** (Scheme 1) via the compound (*S*)-(+)-4-phenyl-2-oxazolidinone **8** [10–18]. However, we did not obtain any β-lactam, but enamine compounds **4** and **5** were obtained with high (*E*)/(*Z*) selectivity and in high yield (Scheme 2).

Results and discussion

The synthesis began with N-acylation, which involved reacting (*S*)-(+)-4-phenyl-2-oxazolidinone **8** with propanoyl chloride in the presence of triethylamine to afford *N*-propanoyl oxazolidinone **9** [19–22] as a white solid in good yield. For the following nucleophilic addition reaction [23–28], a titanium tetrachloride–tertiary amine system was found to be the most effective method for generating the enolate form, which was attacked by the electrophile trimethoxymethane [29–31] to give the intermediate **10** in high yield (Scheme 2).

Compound **10** was hydrolyzed to give the aldehyde intermediate **15** which was successfully condensed with glycine methyl ester hydrochloride to give eneglycinates **4** (Scheme 2) in high yield. When **4** was treated with ethyl 3-hydroxybutyrate in the presence of LiHMDS, the expected nucleophilic addition product **13** was not

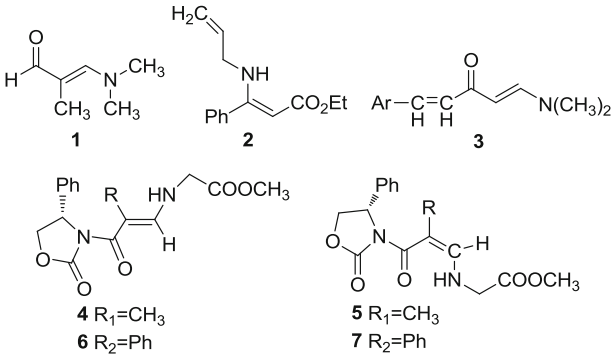
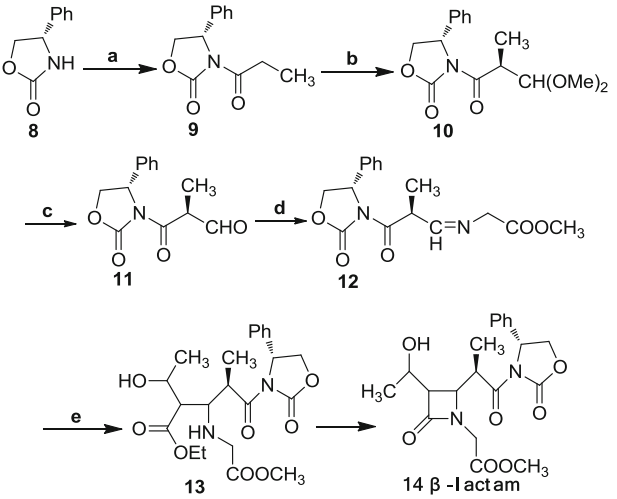
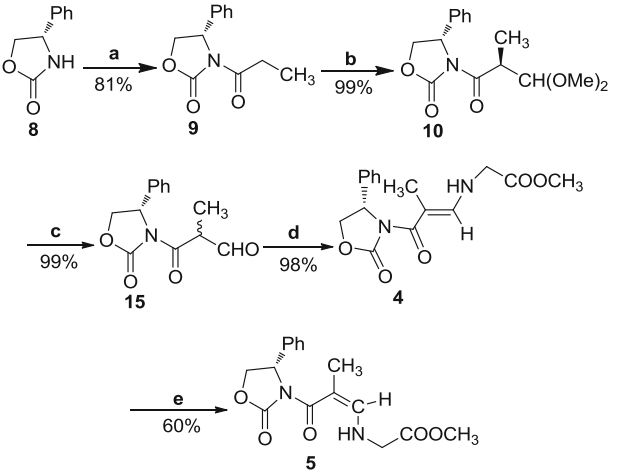


Fig. 1 Reported enamine derivatives **1**, **2**, and **3** and new compounds **4**, **5**, **6**, and **7**



Scheme 1 Original route for synthesis of β-lactams: (*a*) CH_3CH_2COCl, Et_3N, toluene, rt ~50 °C; (*b*) $CH(OMe)_3$, $TiCl_4$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C; (*c*) TFA + AcOH + H_2O 1:4:1, 25 °C; (*d*) glycine methyl ester hydrochloride, $NaHCO_3$, $MgSO_4$, CH_2Cl_2, reflux; (*e*) ethyl 3-hydroxybutyrate, LiHMDS, THF, rt ~−20 °C



Scheme 2 Stereoselective synthesis of (*E*)/(*Z*)-eneglycinates: (*a*) CH_3CH_2COCl, Et_3N, toluene, rt ~50 °C; (*b*) $CH(OMe)_3$, $TiCl_4$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C; (*c*)TFA + AcOH + H_2O 1:4:1, 25 °C; (*d*) glycine methyl ester hydrochloride, $NaHCO_3$, $MgSO_4$, CH_2Cl_2, reflux; (*e*) ethyl 3-hydroxybutyrate, LiHMDS, THF, rt ~−20 °C

obtained, but a new compound **5** was obtained. It was surprising that **5** was not detected in the reaction of **15** to give **4**, but approximately 60 % of **4** was converted to **5** by treatment with LiHMDS and ethyl 3-hydroxybutyrate for 4 h and 40 % of **4** remained unreacted. The structures of compounds **4** and **5** were confirmed by ESI MS, ^1H NMR and ^{13}C NMR spectroscopy, HSQC, among other techniques. They

have the same formula, $C_{16}H_{16}N_2O_5$, but their ^1H and ^{13}C chemical shifts of NH, C=, and CH= (Table 1) were different, so they are geometric isomers.

As seen from Fig. 2, the (*E*)/(*Z*) configuration was determined by ^1H–^1H COSY. For stereoisomer **4**, no correlations were observed between H(1) and H(3). So, the methyl group was far from the olefinic hydrogen, and **4** was the (*E*)-configuration. For **5**, H(2) had no correlation with H(1), but a clear correlation between H(1) and H(3) was observed, with the coupling constant $J = 1{,}500$ MHz. So, the methyl group was close to the olefinic hydrogen, and **5** was the (*Z*)-configuration.

The conditions for conversion of **4** to **5** were also studied (Table 2). When LiHMDS was replaced by $NaN(TMS)_2$, **5** was obtained with high selectivity (Entry 2). However, when the reaction was performed in the absence of ethyl 3-hydroxybutyrate, **5** could not be isolated from the reaction mixture (Entries 3 and 4). Therefore, ethyl 3-hydroxybutyrate was a crucial component for conversion of **4** to **5**.

Considering that the size of the substituents at the α-position of the aldehyde may affect (*E*)/(*Z*) selectivity, the methyl group at the α-position of the aldehyde was replaced by a phenyl group for further research. However, a mixture of **6** and **7** in 1:1 ratio was obtained by the same route (Scheme 3). This means that a bulky substituent at the α-position of the aldehyde will reduce the (*E*)/(*Z*) selectivity of the C–C double bond.

Proposed mechanism

The software MMFF94 was used to calculate the molecular mechanics and force fields of these compounds. As shown in Fig. 3, the preferred conformations of geometric structures of **4** and **5** exist in "non-planar" and "planar" forms (Fig. 3). A possible mechanism was proposed for conversion of **4** to **5** (Scheme 4).

First, ethyl 3-hydroxybutyrate was treated with LiHMDS to form the complex ion **B**, and (*E*)-**4** was also attacked by LiHMDS to afford the "non-planar" transition state **A**. The hydrogen of the complex ion **B** then chelated with the carbonyl group (**α**) of compound **4** to give **C**. Intermolecular and intramolecular hydrogen bonding then led to a conformational change forming the "planar" transition state **D**, because of strong steric hindrance between the facial of benzene and the six-membered ring containing imine double bond. The change in the orientation of the carbonyl group (**β**) and the hydrogen bond will have a direct effect on the

Table 1 ^1H NMR, ^{13}C NMR, and HSQC assignments of compounds **4** and **5** (in $CDCl_3$)

Group	δ_H (**4**)	δ_C (**4**)	δ_H (**5**)	δ_C (**5**)
NH	5.10–5.18		3.01	
C=		99.55		110.55
CH=	7.23–7.26	150.80	6.93	138.67

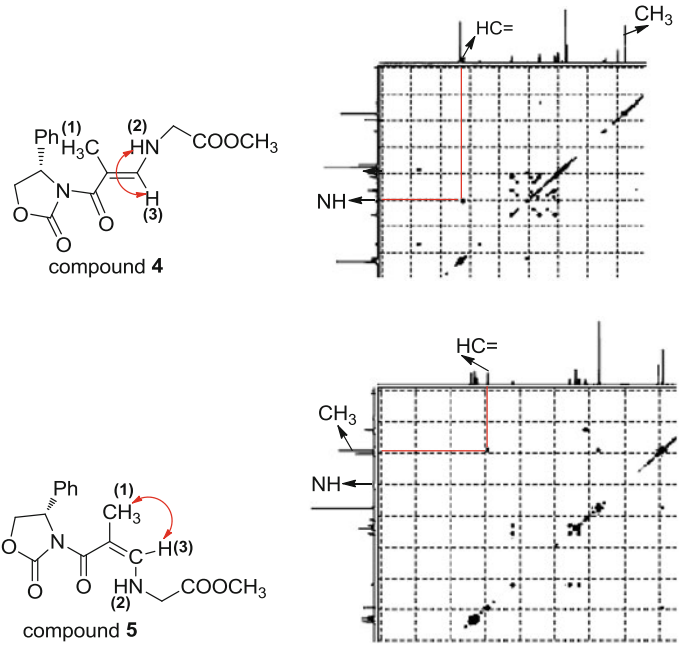


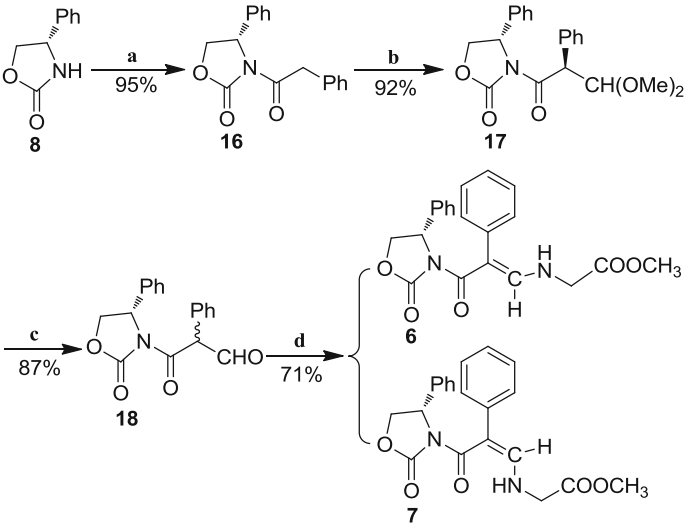
Fig. 2 ^{1}H–^{1}H COSY of compounds **4** and **5**

Table 2 Effect of base on product yields

Entry	Reaction conditions	Results (yield)
1	LiHMDS, ethyl 3-hydroxybutyrate, rt ~−20 °C.	(*Z*)-Product (60 %)
2	$NaN(TMS)_2$, ethyl 3-hydroxybutyrate, rt ~−20 °C.	(*Z*)-Product (60 %)
3	LiHMDS, rt ~−20 °C.	Trace
4	$NaN(TMS)_2$, rt ~−20 °C .	Trace

stereochemical outcome of the reaction. Finally, through post-after the (*Z*)-configuration was formed.

The preferred conformation of (*Z*)-**7** and (*E*)-**6** is depicted in Fig. 4 to explain the effect of the α-phenyl group on stereoselectivity. The energy of the (*E*) configuration, **6**, (85.7 kcal/mol) was higher than that of the (*Z*) configuration, **7**, (75.8 kcal/mol), and the carbonyl groups of **7** and **6** were also present as the "planar" and "non-planar" forms, respectively. At reflux temperature, however, equilibrium was achieved. So, the condensation was mainly controlled by thermodynamic factors. That was why we could not find pure (*Z*)-**7** or (*E*)-**6** in the reaction mixture (Scheme 3).



Scheme 3 Phenyl-substituted synthetic route: (*a*) $PhCH_2COOH$, pivaloyl chloride, Et_3N, toluene, 110 °C; (*b*) $CH(OMe)_3$, $TiCl_4$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C; (*c*) TFA + AcOH + H_2O 1:4:1, 50 °C; (*d*) glycine methyl ester hydrochloride, $NaHCO_3$, $MgSO_4$, CH_2Cl_2, reflux

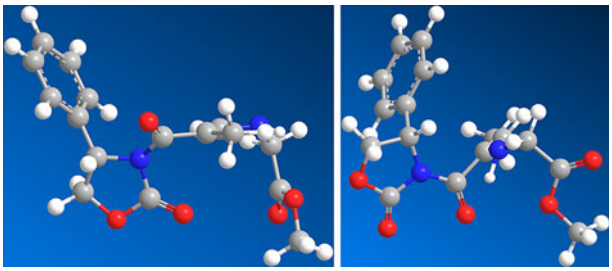
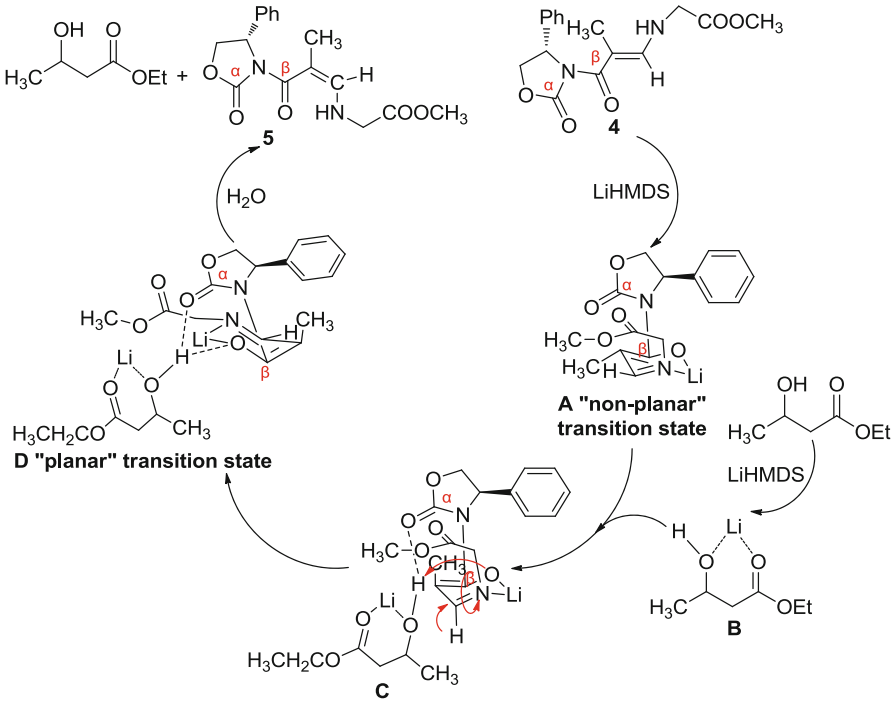


Fig. 3 Geometric structures (MMFF94) and conformations of **4** and **5**

Experimental

General information

Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers and were used without further purification. For thin-layer chromatography (TLC), silica gel plates (GF254) were used and compounds were visualized by irradiation with UV light. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AV-300 or Bruker AV-500 instrument with TMS as internal standard. All chemical shifts (δ) are given in parts per million. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, or m = multiplet). Melting points were determined with a Melt-Temp II apparatus and are reported without correction. IR spectra were recorded on a



Scheme 4 Possible mechanism for conversion of **4** to **5**

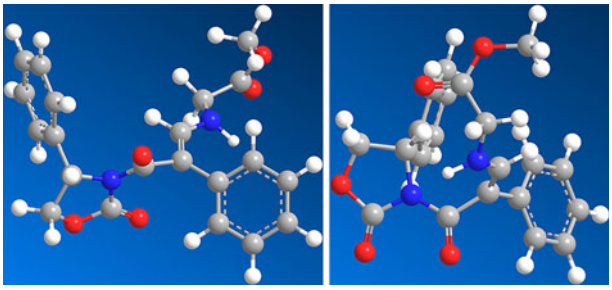


Fig. 4 (Color figure online) Geometric structures (MMFF94) of compounds **6** and **7**

Nicolet iS10 Avatar FT-IR spectrometer, as KBr disks. High-resolution mass spectra (HRMS) were recorded on a Waters Q-TOF micro mass spectrometer.

General synthesis of intermediates and target compounds

(S)-4-Phenyl-3-propionyloxazolidin-2-one ***(9)***

(*S*)-(+)-4-Phenyl-2-oxazolidinone **8** (50 g, 307 mmol), propanoyl chloride (48.2 g, 521 mmol), and toluene (250 mL) were mixed at room temperature and Et_3N

(55.8 g, 552 mmol) was added dropwise. The reaction mixture was stirred at 50 °C for 1 h. When reaction was complete it was quenched with 5 % $NaHCO_3$ then extracted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Isopropyl alcohol (30 mL) was added into the residue at 0–5 °C and the precipitated solid was isolated by filtration to give the product as a white powder (55 g), yield 81 %. m.p. 77–79 °C; $[\alpha]_D^{20}$ +70.3 (*c*, 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11 (t, $J = 7.3$ Hz, 3H), 2.87–3.03 (m, 2H), 4.28 (dd, $J = 3.4$, 8.8 Hz, 1H), 4.69 (dd, $J = 8.8$, 8.8 Hz, 1H), 5.42 (dd, $J = 3.4$, 8.8 Hz, 1H), 7.26–7.40 (m, 5H); HRMS (ESI) calcd for $C_{12}H_{14}NO_3$ $(M + H)^+$: 220.0974, found: 220.0974.

(S)-3-(3,3-Dimethoxy-2-methylpropanoyl)-4-phenyloxazolidin-2-one ***(10)***

$TiCl_4$ (28 g, 15 mmol) and DIPEA (19 g, 15 mmol) were added dropwise at 0 °C to compound **6** (30 g, 148 mmol) in CH_2Cl_2 (300 mL). The solution was maintained at this temperature for 30 min then $CH(OMe)_3$ (18.8 g, 178 mmol) was added. The mixture was warmed to room temperature and stirred for 3 h. After dilution with EtOAc, the organic phase was washed with saturated brine, dried, and concentrated under vacuum. The crude product (40 g, 99 %) was obtained as a white solid and used directly in the next step without purification. A pure sample was obtained by crystallization from isopropyl alcohol. m.p. 73–75 °C; $[\alpha]_D^{20}$ +42.2 (*c*, 0.11, $CHCl_3$); ^{1}H NMR (300 MHz $CDCl_3$) δ (ppm): 1.16 (d, $J = 6.3$ Hz, 3H), 3.16 (s, 3H), 3.29 (s, 3H), 4.20–4.26 (dd, $J = 4.7$, 8.9 Hz, 1H), 4.34–4.42 (m, 2H), 4.68 (dd, $J = 8.9$, 8.9 Hz, 1H), 5.46 (dd, $J = 4.7$, 8.9 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.33, 38.27, 49.49, 53.41, 55.59, 67.42, 74.46, 74.89, 75.31, 103.88, 123.78, 126.30, 126.73, 136.47, 151.33, 171.70; IR (KBr): 2972, 2937, 2836, 1652, 1782, 1698, 1041, 946, 760, 703 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NNaO_5$ $(M + Na)^+$: 316.1161, found: 316.1165.

2-Methyl-3-oxo-3-((S)-2-oxo-4-phenyloxazolidin-3-yl)propanal ***(15)***

Compound **10** (5.9 g, 20 mmol) was dissolved in 50 mL of a 4:1:1 mixture of AcOH, TFA, and H_2O at 35 °C and the solution was stirred for 6 h. After dilution with EtOAc, the organic phase was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude product was obtained as a white foam (4.9 g, 98 %) and used without purification in the next step. A pure sample was obtained by chromatography on silica gel (eluent: hexane–EtOAc 3:1). m.p. 107–108 °C; $[\alpha]_D^{20}$ +78.9 (*c*, 0.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.34 (dd, $J = 3.5$, 3.6 Hz, 3H), 4.26–4.35 (m, 1H), 4.64 (q, $J = 7.3$ Hz, 1H), 4.71–4.78 (m, 1H), 5.44–5.50 (m, 1H), 7.26–7.42 (m, 5H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 8.92, 9.29, 50.96, 50.99, 56.69, 56.81, 69.29, 69.39, 124.82, 124.94, 127.74, 127.86, 128.21, 128.25, 137.39, 137.76, 152.81, 167.88, 168.12, 195.26, 195.72; IR (KBr): 3449, 3134, 2944, 2845, 1788, 1739, 1689, 1059, 940, 757, 700 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}NO_4$ $(M + H)^+$: 248.0923, found: 248.0925.

*Preparation of (S,E)-methyl 2-[2-(2-oxo-4-phenyloxazolidine-3-carbonyl)prop-1-enylamino]acetate **(4)***

A mixture of aldehyde intermediate **15** (7 g, 28 mmol), $NaHCO_3$ (7.1 g, 85 mmol), $MgSO_4$ (11.9 g, 99 mmol), and glycine methyl ester hydrochloride (4.2 g, 34 mmol) was dissolved in CH_2Cl_2 (70 mL). The mixture was heated under reflux, with stirring, for 3 h. The mixture was then filtered and the filtrate was concentrated to give the product as a white foam (6.8 g), yield: 97 %. m.p. 124–125 °C; $[\alpha]_D^{20}$ +46.9 (*c*, 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.70 (s, 3H), 3.74 (s, 3H), 3.98 (d, $J = 5$ Hz, 2H), 4.11 (dd, $J = 9.0$, 18.0 Hz, 1H), 4.63 (dd, $J = 8.6$, 17.2 Hz, 1H), 5.19 (dd, $J = 9.0$, 18.2 Hz, 1H), 5.58 (dd, $J = 9.1$, 9.1 Hz, 1H), 7.24 (s, 1H), 7.29–7.33(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.05, 48.89, 52.44, 59.09, 69.64, 99.55, 126.59, 128.57, 129.00, 137.72, 150.80, 155.34, 168.74, 170.20; IR (KBr): 3351, 2961, 2360, 1757, 1620, 1205, 762, 701 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_5$ $(M + H)^+$: 319.1294, found: 319.1299.

*Preparation of (Z)-methyl 2-[2-(2-oxo-4-phenyloxazolidine-3-carbonyl)prop-1-enylamino]acetate **(5)***

A solution of ethyl 3-hydroxybutyrate (30 mg, 0.2 mmol) in THF was added dropwise to a solution of LiHMDS (1 mol L^{-1} in THF, 0.2 mL) at −20 °C over a period of 30 min. A solution of compound **4** (50 mg, 0.2 mmol) in THF (5 mL) was then added and the mixture was stirred at this temperature for 15 min, then stirred for 4 h at room temperature, the reaction was quenched by addition of aqueous HCl (1 M). The reaction mixture was extracted three times with EtOAc. The organic phase was washed with $NaHCO_3$ solution, phosphate buffer (pH 7), and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude product which was purified by column chromatography (hexane–EtOAc 1:1) to give colorless oil (18 mg), yield 60 %. $[\alpha]_D^{20}$ +70.0 (*c*, 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.91 (d, $J = 1$ Hz, 3H), 3.74 (s, 3H), 4.30 (dd, $J = 5.0$, 11.5 Hz, 1H), 4.39 (d, $J = 6.5$ Hz, 1H), 4.55–4.59 (dd, $J = 8.0$, 12.0 Hz, 1H), 6.21 (dd, $J = 5.0$, 5.0 Hz, 1H), 6.93 (d, $J = 1$ Hz, 1H), 7.22–7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.98, 14.07, 49.66, 52.64, 58.17, 60.28, 62.08, 110.55, 127.44, 127.66, 128.23, 136.71, 138.67, 151.87, 164.44, 167.99; IR (KBr): 3454, 3066, 2954, 2359, 1754, 1701, 1214, 770, 700 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_5$ $(M + H)^+$: 319.1294, found: 319.1306.

*(S)-4-Phenyl-3-(2-phenylacetyl)oxazolidin-2-one **(16)***

(*S*)-(+)-4-Phenyl-2-oxazolidinone **8** (10 g, 61 mmol), phenylacetic acid (16.7 g, 123 mmol), and Et_3N (24.8 g, 245 mmol) were dissolved in 130 mL anhydrous toluene under N_2 (g) and warmed to 80 °C. Pivaloyl chloride (14.8 g, 123 mmol) in toluene (0.2 mL $mmol^{-1}$, 25 mL) was dropwise over a period of 30 min, then the solution was heated under reflux, with stirring, for 5 h. When the reaction was

complete it was quenched with 2 mol L^{-1} HCl solution, and extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated to give crude product, which was recrystallization from isopropyl alcohol to give a white powder (5.8 g, 95 %). $[\alpha]_D^{20}$ +82.3 (*c*, 0.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.24 (dd, $J = 3.9$, 8.9 Hz, 3H), 4.28 (s, 2H), 4.66 (dd, $J = 8.8$, 8.8 Hz, 1H), 5.41 (dd, $J = 3.8$, 8.7 Hz, 1H), 7.18–7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.61, 57.73, 69.87, 125.94, 127.14, 128.47, 128.67, 129.10, 129.70, 133.35, 138.84, 153.63, 170.53; IR (KBr): 3409, 3134, 3029, 1765, 1714, 775, 736, 711, 699 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}NNaO_3$ $(M + Na)^+$: 304.0950, found: 304.0942.

(S)-3-[(S)-3,3-Dimethoxy-2-phenylpropanoyl]-4-phenyloxazolidin-2-one ***(17)***

Compound **16** (16.3 g, 58 mmol), $TiCl_4$ (11.6 g, 61 mmol), and *N*,*N*- diisopropylethylamine (7.5 g, 58 mmol), $CH(OMe)_3$ (7.4 g, 70 mmol) were dissolved in anhydrous CH_2Cl_2 (100 mL) as described for compound **10**. The product was recrystallized from isopropyl alcohol to give a white powder (14.7 g, 71 %). $[\alpha]_D^{20}$ +78.5 (*c*, 0.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.16 (s, 3H), 3.20 (s, 3H), 4.14 (dd, $J = 4.2$, 8.8 Hz, 1H), 4.52 (dd, $J = 8.8$, 8.8 Hz, 1H), 4.93 (d, $J = 8.8$ Hz, 1H), 5.32 (dd, $J = 4.2$, 8.8 Hz, 1H), 5.63 (d, $J = 8.8$ Hz, 1H), 7.24–7.38 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 50.68, 51.45, 54.67, 56.78, 68.47, 105.20, 124.78, 126.82, 127.48, 127.56, 127.98, 128.47, 133.26, 137.74, 152.36, 170.05; IR (KBr): 3447, 3128, 3017, 2917, 2836, 2360, 1773, 1703, 753, 763, 715, 700 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}NNaO_5$ $(M + Na)^+$: 378.1317, found: 378.1318.

3-Oxo-3-((S)-2-oxo-4-phenyloxazolidin-3-yl)-2-phenylpropanal ***(18)***

Compound **17** (5 g, 14 mmol) was dissolved in 50 mL of a 4:1:1 mixture of AcOH, TFA, and H_2O at 50 °C and stirred for 6 h. The reaction mixtures were worked up as described in the general procedure for compound **15** to give white foam (3.8 g, 87 %). $[\alpha]_D^{20}$ +125.9 (*c*, 0.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.19–4.27 (m, 1H), 4.60–4.72 (m, 1H), 5.37–5.50 (m, 1H), 5.88 (d, $J = 12.2$ Hz, 1H), 7.11–7.44 (m, 10H), 9.68–9.69 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 57.72, 57.98, 63.08, 63.21, 70.16, 70.35, 125.87, 126.00, 128.70, 128.75, 128.83, 128.86, 129.07, 129.14, 129.28, 129.47, 129.57, 130.23, 130.49, 138.25, 138.36, 153.41, 153.65, 167.28, 167.52, 193.67, 194.38; IR (KBr): 3427, 3064, 3033, 2922, 2849, 1778, 1705, 762, 700 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}NO_4$ $(M + H)^+$: 310.1079, found: 310.1081.

(S,E)-Methyl 2-((3-oxo-3-(2-oxo-4-phenyloxazolidin-3-yl)-2-phenylprop-1-en-1-yl)amino)acetate and (S,Z)-methyl 2-((3-oxo-3-(2-oxo-4-phenyloxazolidin-3-yl)-2-phenylprop-1-en-1-yl)amino)-acetate ***(6 and 7)***

Aldehyde intermediate **18** (3.8 g, 12 mmol), $NaHCO_3$ (3.1 g, 37 mmol), $MgSO_4$ (5.2 g, 43 mmol), and methyl ester hydrochloride (1.8 g, 15 mmol) were dissolved

in CH_2Cl_2 (80 mL) at room temperature. The mixture was heated under reflux for 3 h. After filtration, the filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: hexane–EtOAc 2:1) to furnish a yellow oil (3.3 g, 71 %). $[\alpha]_D^{20}$ +40.0 (*c*, 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.73 (d, $J = 0.5$ Hz, 6H), 3.91–3.93 (m, 4H), 4.05–4.15 (m, 3H), 4.48–4.51 (dd, $J = 9.0$, 9.0 Hz, 1H), 4.58–4.61 (dd, $J = 9.0$, 9.0 Hz, 1H), 5.25–5.28 (dd, $J = 8.0$, 16.5 Hz, 2H), 5.31(s, 1H), 5.51–5.54 (dd, $J = 9.0$, 18.0 Hz, 1H), 6.77 (s, 1H), 6.79 (s, 1H), 7.05–7.30 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 48.94, 49.57, 52.53, 52.53, 58.89, 58.99, 69.44, 69.54, 104.90, 107.04, 125.85, 126.90, 127.11, 127.29, 128.24, 128.66, 128.75, 128.85, 129.00, 129.03, 129.13, 129.41, 130.38, 133.95, 137.76, 137.79, 138.88, 149.74, 155.36, 168.07, 168.91, 169.27, 169.81; IR (KBr): 3392, 3143, 2360, 2342, 1773, 1648, 763, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}N_2O_5$ $(M + H)^+$: 381.1450, found: 318.1457.

Conclusions

Herein we have reported a convenient and stereoselective method for synthesis of new building blocks (*E*) or (*Z*)-(*N*-acyl-oxazolidinone)-eneglycinates. According to MMFF94, the carbonyl groups of eneglycinates have a "planar" or "non-planar" configuration in the presence of ethyl 3-hydroxybutyrate, which results in stable thermodynamic or kinetic controlled products.

When the (*E*) and (*Z*) configurations were achieved at equilibrium ratio in the reaction mixture, the "steady-state" was not affected by the amount of the base and glycinates. Transformation of the thermodynamic product to the kinetic product was investigated, and a mechanism was proposed by use of molecular mechanics. All the intermediates were purified after simple crystallization with excellent yields, and the reactions could be performed safely on a large scale.

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