A Mild and Highly Efficient Synthesis of Chiral *N*-Dichloroacetyl-4-ethyl-1,3-oxazolidines

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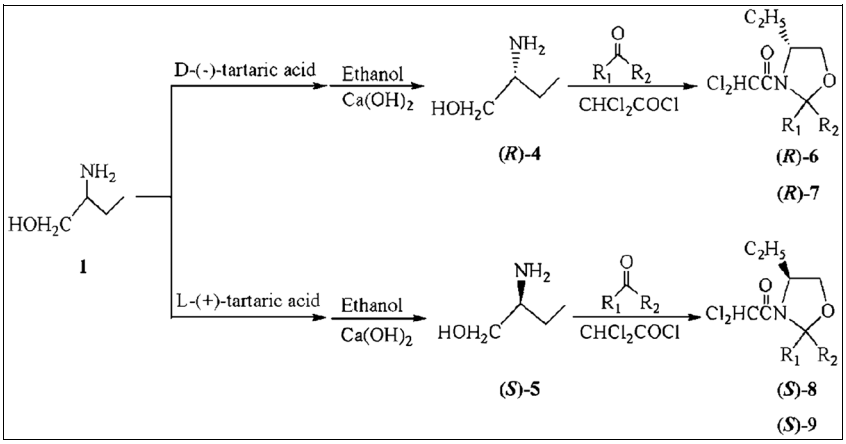

Chiral 2-amino-butanols (**4** and **5**) were obtained *via* the isolation of diastereomeric salt. Then, chiral compounds (**6–9**) were synthesized by a sequential procedure involving condensation of chiral 2-amino-butanol with ketone and dichloroacetyl chloride. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and element analysis. The absolute configurations of (*S*)-**8** was determined by X-ray crystallography.

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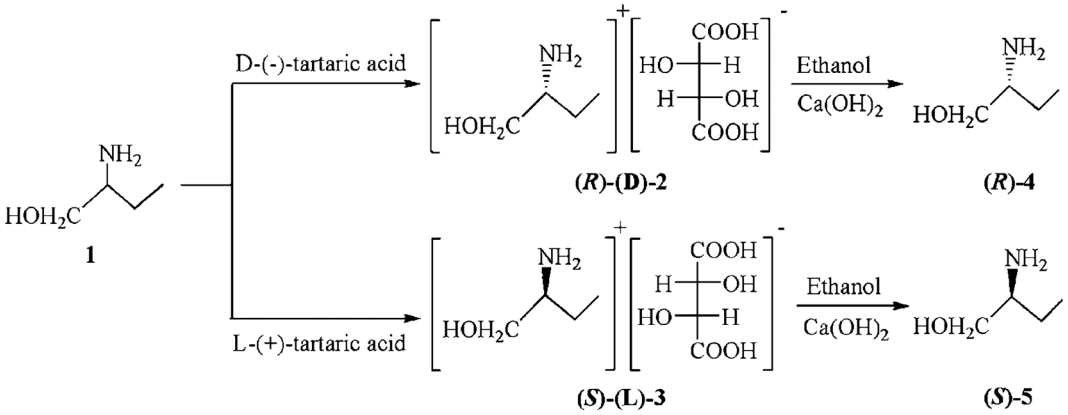
INTRODUCTION

Substituted oxazolidines are important heterocycles bearing remarkable biological activities. It has previously been shown that the *N*-dichloroacetyl oxazolidine as herbicide safener has attracted widespread attention in agricultural biochemistry [1]. According to the theory of structure–activity relationships, the introduction of different alkyl groups to the oxazole ring often resulted in the change of activities of the compounds as herbicide safener. Consequently, the synthesis of oxazolidine derivatives with many applications was observed in the literature [2,3] and lots of *N*-dichloroacetyl oxazolidine derivatives were obtained in good yields *via* a sequential procedure, including cycloaddition, condensation, and acylation [4,5]. Some substituted oxazolidines were chiral compounds and their biological activity often related with their chirality [6–8]. Because of the importance of this class of compounds, many methods of preparation of chiral oxazolidines were reported [9,10]. Taking into account these findings and considering the results of previously reported studies, this study was focused on the preparation of series of chiral *N*-dichloroacetyl-4-ethyl-oxazolidine derivatives by a milder and more efficient method.

Optically active amino alcohols are important building blocks for the synthesis of chiral *N*-dichloroacetyl oxazolidine derivatives. In organic compounds, chiral structure is profoundly important because the first enantiomer of racemic compounds may have biological activity, whereas the second enantiomer may not have this property. Some of the known methods to obtain optically active compounds include resolution of racemic mixture [11] and asymmetric reduction of chiral compounds [12]. Bai *et al*. reported the methods for the enantioseparation of racemic amino alcohols by chiral tartaric acid which required harsh conditions, such as high temperature and longer reaction time [13]. Boldt *et al*. reported a highly enantioselective resolution of α-dihydrotetrabenazine using di-*p*-toluoyl-L-tartrate and di-*p*-toluoyl-D-tartrate in low yields [14]. A wide variety of *N*-protected chiral amino alcohol was prepared in high yields by asymmetric reduction of *N*-carboxyanhydride (UNCAs) amino acid derivatives [15]. The preparation of chiral alcohols was achieved by combining lipase-catalyzed resolution with the Mitsunobu reaction [16]. In addition, the enzymatic conversions [17], asymmetric dihydroxylation [18], asymmetric Henry reaction [19], and other methods [20] were also been used to obtain nonracemic compounds. However, these methods suffered from some drawbacks, especially the use of expensive reagents. In addition, these methods involved multistep

Scheme 1. Route for the synthesis of (***R***)-**4** and (***S***)-**5**.



synthetic operations which lower the overall yields. In this article, an easy and fast method for the enantioseparation of racemic amino alcohols was reported. Then, chiral title compounds were synthesized by a sequential procedure involving condensation of chiral 2-amino-butanol with ketone and dichloroacetyl chloride. Following this route, which allowed the introduction of alkyl group onto the oxazole ring, four new chiral *N*-dichloroacetyl-4-ethyl-oxazolidine derivatives were synthesized.

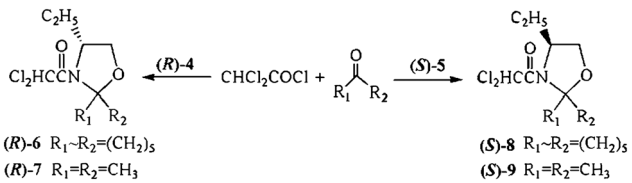
RESULTS AND DISCUSSION

In the present study, chiral intermediates, (***R***)-**4** and (***S***)-**5**, were obtained in 43.2–43.9% yields, separately, and high optical purity (Scheme 1). In the enantioseparation, the main factors influencing the yield and optical purity were the crystallization temperature, crystallization time, and the ratio of reactants in the preparation of diastereomeric salt (***R***)-(**D**)-**2** and (***S***)-(**L**)-**3** crystals.

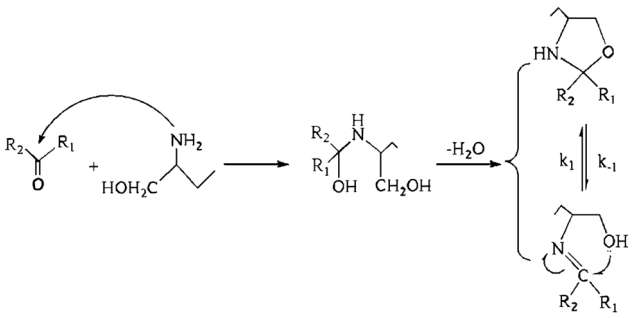
The crystallization temperature seemed to be crucial to obtain good yield. It was noteworthy that the higher the crystallographic temperature, the less the yields and the better optical purity of the crystals. It was inferred that high temperature could increase the solubility of the crystals in solvent. To obtain crystals with high yield and good optical purity, the crystallization temperature was optimized at 10–20°C. Crystallization time also influenced the yields. Logically the yield could be increased by prolonging the crystallization time, but not the optical purity. According to the results, the best crystallization time to obtain (***R***)-(**D**)-**2** and (***S***)-(**L**)-**3** crystals was 24 h. Some decrease in yield was observed when crystallization with short time; however, some decrease in optical purity was observed when crystallization with long time. The reason was that the long crystallization time enhanced the formation of crystal, but at the meantime, the formation of large amount of crystals decreased the purity of crystals. In addition, the optimum ratio of reactants was determined from the optical purity of (***R***)-(**D**)-**2** and (***S***)-(**L**)-**3** crystals. The results showed that the optimum ratio of reactants was 1:1 between racemic 2-amino-butanol and chiral tartaric acid. The unsuitable ratio of reactants frequently led to the decrease of the optical purity of crystals. So, it was concluded that higher or lower ratio of reactants could enhance the formation of impure crystal.

Then, chiral *N*-dichloroacetyl-4-ethyl-oxazolidines were synthesized by a sequential procedure involving condensation of chiral intermediate (***R***)-**4** or (***S***)-**5** with ketone and acylation with dichloroacetyl chloride (Scheme 2). Chiral intermediates (***R***)-**4** and (***S***)-**5** were successfully condensed with ketone (cyclohexanone or acetone) to afford chiral oxazolidine without any catalyst. The possible mechanism of this reaction is depicted in Scheme 3 [21]. The first step of this reaction was the nucleophilic addition of amino and the carbonyl to form an aminodiol. Then, the addition product converted into oxazolidine existed in equilibrium with open-chain imine, but the formation of oxazolidine is rather fast. The rate constant of the cyclization of this open-chain imine was estimated as $k_1 > 0.06\ s^{-1}$ and it could be increased when passing from the neat liquids to solutions. The increase might be attributable to the disruption of the intermolecular hydrogen bonds OH···N stabilizing the open-chain imine. For the same reason, the dilution of the solutions is stabilized the cyclic oxazolidine [22]. To get oxazolidine product, toluene was used as dissolvent. The formation of oxazolidine would be retarded because of the steric hindrance effect of bulky alkyl groups.

Scheme 2. Route for the synthesis of chiral *N*-dichloroacetyl oxazolidines (**6**–**9**).



Scheme 3. Equilibrium between imine and oxazolidines.



Finally, chiral *N*-dichloroacetyl-4-ethyl-oxazolidines were synthesized from chiral oxazolidine by acylation with dichloroacetyl chloride. Low reaction temperature, −5 to 0°C, was used because this reaction was exothermic. To improve the yield of chiral *N*-dichloroacetyl- 4-ethyl-oxazolidine, sodium hydroxide solution was chosen as the attaching acid agent, which reacted with byproduct HCl. To our knowledge, this was the first report to synthesize chiral *N*-dichloroacetyl-4-ethyl-1,3-oxazolidine derivatives. When compared with the reported strategy [14–18], the described procedure offered the advantages of operational simplicity and use of cheap and readily available solvents.

The single crystal of (***S***)-**8** was obtained by dissolving it in the solvent of ethyl acetate and light petroleum, followed by slow evaporation. The molecular structure of (***S***)-**8** was confirmed by X-ray crystallography (Fig. 1). A crystal of dimensions of 0.20 mm × 0.20 mm× 0.16 mm was chosen and the crystallographic data were recorded on a Bruker SMART CCD diffractometer. Measurements were performed at 298 (2) K using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The cell parameters were determined by using SHELX-97 software. The X-ray structure analysis indicated that (***S***)-**8** contains one chiral center-C10, and the configuration was S. This compound consisted of one cyclohexane ring and one oxazole ring. The dihedral angle between these two rings was 82.3°. Crystallographic data (excluding structure factors) for the structure in this article were deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 757316. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Each request should be accompanied by the complete citation of this article.

In summary, the aforementioned protocol has developed an convenient synthetic method for the preparation of chiral *N*-dichloroacetyl oxazolidines. Four chiral *N*-dichloroacetyl-4-ethyl-oxazolidine compounds were synthesized from readily available and inexpensive starting materials. The molecular structure of (***S***)-**8** was determined by single-crystal X-ray diffraction.

EXPERIMENTAL

The melting points were determined on Beijing Taike melting point apparatus (X-4) and uncorrected. The infrared (IR) spectra were taken on a KJ-IN-27G infrared spectrophotometer (KBr). The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AVANVE 300 MHz nuclear magnetic resonance spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. The elemental analysis was performed on FLASH EA1112 elemental analyzer.

Diffraction data of compound (***S***)-**8** was measured on a Bruker SMART CCD diffractometer at 298 (2) K using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å).

General procedure for the preparation of chiral intermediate (*R*)-4 and (*S*)-5. Chiral tartaric acid (0.20 mol) was dissolved in a small amount of distilled water and racemic 2-amino-butanol (0.40 mol) was added dropwise with stirring and cooling in an ice bath. The solution was placed in dark place at 10–20°C temperature for 24 h. After the crystallization of diastereomeric salt (***R***)-(**D**)-**2** or (***S***)-(**L**)-**3**, the mixture was filtered and the crystals were washed by ethanol and then dried. Afterward, (***R***)-(**D**)-**2** or (***S***)-(**L**)-**3** (20 g) was dissolved in a small amount of distilled water and $Ca(OH)_2$ was added with stirring until pH 10.6. The mixture was filtered and the filtrate was collected and vacuum distilled to obtain chiral intermediate (***R***)-**4** and (***S***)-**5**.

General procedure for the synthesis of chiral *N*-dichloroacetyl oxazolidine 6–9. Chiral amino alcohol (0.067 mol) and 0.067 mol of the ketone (cyclohexanone or acetone) were mixed with 20 mL of methylbenzene. The reaction mixture was stirred at 33–34°C for 1 h. Then, the mixture was cooled to 0°C and 10.0 mL of 33% sodium hydroxide solution was added. Afterward, 7.3 mL (0.076 mol) of dichloroacetyl chloride was added dropwise with stirring in a cold ice bath. Stirring was continued for 3 h.

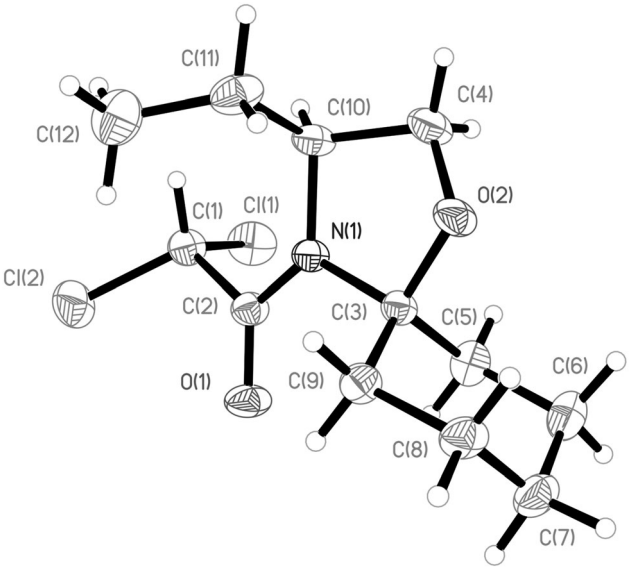


Figure 1. A view of (***S***)-**8** showing the atom-numbering scheme.

The organic phase was rinsed with water until pH 7. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed by distillation under normal pressure. The crude products **6** and **8** were recrystallized with ethyl acetate and light petroleum until the white crystals were obtained. The crude products **7** and **9** were purified on silica gel by column chromatography.

(R)-2-Amino-butanol (4). Yield: 43.2%; colorless oil; $[\alpha]_D^{20}$ (c = 1, H_2O) = −9.2°; IR (KBr): 3356–3296 (O-H, N-H), 1583–1461 (O-H, N-H), 1080–1047 (O-C, N-C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): δ (ppm) 3.25–3.61 (m, 2H, -NH_2), 2.73–2.77 (m, 1H, -OH), 2.12 (s, 3H, -N-CH-, -CH_2-O), 1.26–1.49 (m, 2H, C-CH_2-C), 0.92–0.97 (t, J = 7.38 Hz, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ (ppm) 66.37, 54.37, 27.25, 10.47; Anal. Calcd for $C_4H_{11}NO$: C, 53.90; H, 12.44; N, 15.71%. Found: C, 53.96; H, 12.39; N, 15.67%.

(S)-2-Amino-butanol (5). Yield: 43.9%; colorless oil; $[\alpha]_D^{20}$ (c = 1, H_2O) = +9.8°; IR (KBr): 3356–3296 (O-H, N-H), 1583–1461 (O-H, N-H), 1080–1047 (O-C, N-C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): δ (ppm) 3.25–3.62 (m, 2H, -NH_2), 2.74–2.77 (m, 1H, -OH), 1.93 (s, 3H, -N-CH-, -CH_2-O), 1.27–1.50 (m, 2H, C-CH_2-C), 0.94–0.98 (t, J = 7.42 Hz, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ (ppm) 66.48, 54.37, 27.40, 10.47; Anal. Calcd for $C_4H_{11}NO$: C, 53.90; H, 12.44; N, 15.71%. Found: C, 53.85; H, 12.42; N, 15.70%.

(R)-N-Dichloroacetyl-3-ethyl-1-oxa-4-aza-spiro-4.5-decane (6). Yield: 63.7%; white crystal; mp 101–102°C; $[\alpha]_D^{20}$ (c = 2, $CHCl_3$) = -7.5°; IR (KBr): 1663 (C═O), 1123 (N-C-O), 1109 (-CH_2-O-C-), 802 (C-Cl), 655 (N-C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): δ (ppm) 6.07 (s, 1H, Cl_2CH-), 3.87–3.96 (m, 2H, -C-CH_2-O-), 3.76–3.81 (m, H, -N-CH-C), 2.34–2.64 (m, 2H, C-CH_2-C), 1.27–1.85 (m, 10H, -$(CH_2)_5$-), 0.96–1.00 (t, J = 7.41 Hz, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ (ppm) 160.32, 97.83, 66.33, 65.83, 59.16, 34.62, 28.42, 28.16, 24.46, 23.23, 22.99, 10.80; Anal. Calcd for $C_{12}H_{19}Cl_2NO_2$: C, 51.44; H, 6.83; N, 5.00%. Found: C, 51.50; H, 6.90; N, 4.95%.

(R)-3-Dichloroacetyl-2,2-dimethyl-4-ethyl-1,3-oxazolidine (7). Yield: 59.3%; colorless oil; $[\alpha]_D^{20}$ (c = 2, $CHCl_3$) = −10.2°; IR (KBr): 1677 (C═O), 1407 (CH_3-C-CH_3), 1130 (-CH_2-O-C-), 810 (C-Cl), 667 (N-C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): δ (ppm) 6.03 (s, 1H, Cl_2CH-), 4.25–4.32 (m, 1H, -N-CH-C), 3.24–4.00 (m, 2H, -C-CH_2-O-), 1.58–2.17 (m, 8H, CH_3-C-CH_3, C-CH_2-C), 1.36–1.38 (d, J = 5.97 Hz, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ (ppm) 159.57, 96.41, 70.72, 66.96, 52.20, 30.95, 25.51, 23.13, 17.76; Anal. Calcd for $C_9H_{15}Cl_2NO_2$: C, 45.02; H, 6.30; N, 5.83%. Found: C, 45.09; H, 6.37; N, 5.75%.

(S)-N-Dichloroacetyl-3-ethyl-1-oxa-4-aza-spiro-4.5-decane (8). Yield: 61.3%; white crystal; mp 101–102°C; $[\alpha]_D^{20}$ (c = 2, $CHCl_3$) = +7.3°; IR (KBr): 1663 (C═O), 1123 (N-C-O), 1109 (-CH_2-O-C-), 802 (C-Cl), 655 (N-C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): δ (ppm) 6.07 (s, 1H, Cl_2CH-), 3.87–3.96 (m, 2H, -C-CH_2-O-), 3.76–3.81 (m, H, -N-CH-C), 2.37–2.64 (m, 2H, C-CH_2-C), 1.51–1.83 (m, 10H, -$(CH_2)_5$-), 0.96–1.01 (t, J = 7.44 Hz, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ (ppm) 160.32, 97.84, 66.33, 65.83, 59.16, 34.62, 28.42, 28.16, 24.46, 23.23, 22.99, 10.80; Anal. Calcd for $C_{12}H_{19}Cl_2NO_2$: C, 51.44; H, 6.83; N, 5.00%. Found: C, 51.47; H, 6.88; N, 5.07%.

(S)-3-Dichloroacetyl-2,2-dimethyl-4-ethyl-1,3-oxazolidine (9). Yield: 60.1%; colorless oil; $[\alpha]_D^{20}$ (c = 2, $CHCl_3$) = +9.7°; IR (KBr): 1680 (C═O), 1417 (CH_3-C-CH_3), 1083 (-CH_2-O-C-), 806 (C-Cl), 667 (N-C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): δ (ppm) 6.08 (s, 1H, Cl_2CH-), 3.78–4.02 (m, 3H, -C-CH_2-O-, -N-CH-C), 1.55–2.17 (m, 8H, CH_3-C-CH_3, C-CH_2-C), 0.96–1.01 (t, J = 7.46 Hz, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 75 Hz): δ (ppm) 160.17, 96.23, 66.68, 65.57, 59.20, 27.98, 26.26, 22.01, 10.41; Anal. Calcd for $C_9H_{15}Cl_2NO_2$: C, 45.02; H, 6.30; N, 5.83%. Found: C, 45.01; H, 6.33; N, 5.70%.

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