Stereocontrol of the Schiff Base of Substituted Benzaldehyde to Staudinger Cycloaddition Reaction

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Syntheses of 4 novel chiral azetidin-2-one derivatives, which were characterized by ^{1}H NMR, IR, specific rotation and elemental analysis, through Staudinger cycloaddition reaction of Schiff base of benzaldehyde with chlorine substitution at different position in benzene ring, were described. For the first time, this type of 3*S*,4*R* configuration azetidin-2-one monocrystals with many chiral centers [(3*S*,4*R*)-3-hydroxy-*N*-[(*S*)-(1-phenyl)ethyl]-4-(2′-chlorophenyl)-azetidin-2-one monocrystal] were obtained, the structures of which were determined by X-ray diffraction analysis. The effects of Schiff base of benzaldehyde with chlorine substitution at different position in benzene ring on stereoselectivity of Staudinger cycloaddition reaction products were discussed and the results are showed as below: 2-chlorophenyl Schiff base favored to yield 3*S*,4*R* configuration product, but 4-chlorophenyl Schiff base favored to yield 3*R*,4*S* configuration product. The reaction orientation of 2,4-dichlorophenyl Schiff base was determined by corporate effect of 2- and 4-chlorine, and that of the 4-chlorine was more obvious. In contrast to 4-chlorophenyl, although the main product was 3*R*,4*S* configuration, 3-chlorophenyl owned lower selectivity.

Keywords Staudinger cycloaddition reaction, azetidin-2-one, stereoselectivity, Schiff base

Introduction

Staudinger cycloaddition reaction is often adopted to synthesize 2-lactam antibiotics pharmaceuticals[1-3] and many other bioactive chemicals. The synthesis of 2-lactam through stereocontrolling is specially conspicuous.[4] At the same time, the increasing of 2-lactam compounds in enzyme inhibiting field has been continuously attracting interests of scientists.[5] In syntheses and semisyntheses of paclitaxel and doxetaxol, Staudinger cycloaddition reaction has been regarded as one of the most effective ways which can introduce chiral groups on Schiff base to synthesize side chains.[6] Due to the syntheses of 2-lactam and its derivatives with bioactivity, the study of Staudinger cycloaddition reaction and corresponding stereoselectivity was continuously deepened and poured into new vigor.[6,7] Recently, employing asymmetric reagents to obtain different chiral azetidin-2-one derivatives via Staudinger cycloaddition reaction has been reported,[8] and some research groups[9] have explored Studinger cycloaddition of asymmetric Schiff base formed through chiral amine. However, the study of the substituted group effects of aromatic aldehydes with chlorine substitution at different position in benzene ring on stereoselectivity of Staudinger cycloaddition reaction has been not reported previously.

In this paper we describe: (1) the acquirement of (*R*,*S*)-2- lactam via Staudinger cycloaddition reaction (Scheme 1) of asymmetric chlorophenyl Schiff base, which was obtained from the reaction of chiral (*S*)-1-phenylethylamine and chlorobenzaldehyde; (2) purification of (*S*,*R*)-2-lactam which was inaccessible in the past and (3) relationships between phenyl with chlorine substitution at different position in benzene ring and stereoselectivity of the products.

Experimental

Apparatus

Melting points were determined on an RY-1 melting point apparatus and uncorrected. Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer. ^{1}H NMR spectra were measured on a Brucker-500 MHz spectrometer using TMS as an internal standard. Optical activity was performed using a Perkin-Elmer 241 MC polarimeter. Mass spectra were recorded on HP1100 HPLC-MSD mass spectrometer.

Preparation of azetidin-2-one derivatives

To a 50-mL flask was added substituted phenylaldehyde (0.011 mol), 15 mL of dichloromethane and 40 nm molecular sieves (2 g). Then (*S*)-1-phenylethylamine (0.010 mol) was quickly added to the mixture. The solution was stirred for 6—12 h at room temperature until the result of TLC showed that chiral amine disappeared. After molecular sieves were filtered, dichloromethane was removed by evaporation to afford light yellow viscose Schiff

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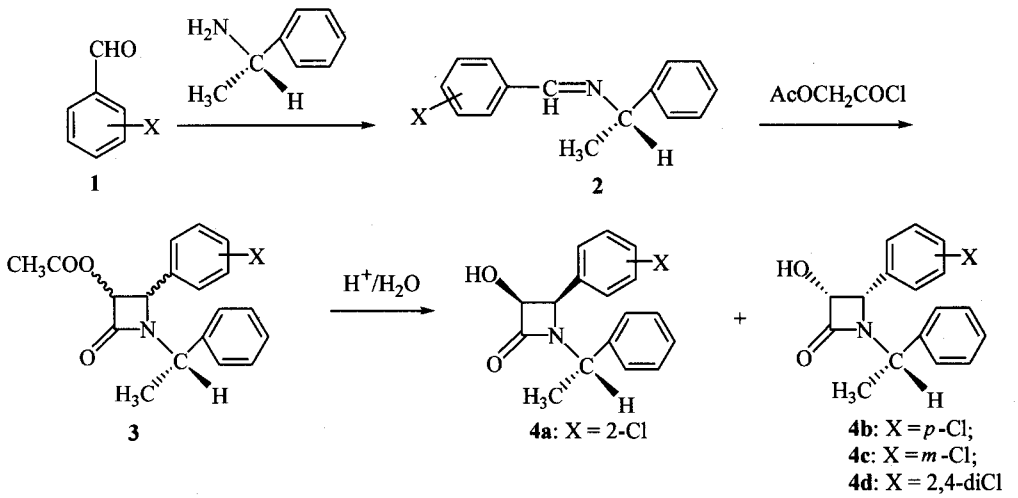
Scheme 1 Syntheses of **4a**, **4b**, **4c** and **4d**



base (not purified).

To a 100-mL three-necked flask was added Schiff base above dissolved in 20 mL of trichloromethane and triethylamine (0.021 mol, 2.9 mL). The mixture was stirred and cooled to −5—0 ℃ in an ice-salt bath, followed by adding dropwise the solution of acetoxyacetyl chloride (0.012 mol, 1.6 mL) and trichloromethane (15 mL). Then after removing the ice-salt bath, the reaction mixture was continued to stir for 2—4 h at room temperature and acidified by 20 mL of HCl (2.7 mol·L^{-1}) solution. The resulting solution was washed twice with water (20 mL) and the organic layer was separated and dried over $MgSO_4$. After removal of the solvent, a brown viscous liquid, 3-acetoxy-4-(substituted phenyl)-2-(1-phenylethyl)-azetidin-2-one, was obtained.

To a 100-mL three-necked flask was added 3 mol·L^{-1} KOH solution (13 mL) and THF (15 mL), then the mixture of product was dropped to above liquid and THF (9 mL) at −1—3 ℃. After being stirred for 2.5 h, the resulting solution was adjusted to pH = 9 by 30 mL of saturated $NaHCO_3$ solution, and the organic layer was extracted three times respectively using 20 mL, 20 mL and 15 mL of ethyl acetate solution, then dried using $MgSO_4$. After removal of solvent, a yellow solid was obtained. The target product and its isomer were purified by recrystallization.

Synthesis of [(3*S*,4*R*)-3-*hydroxy*-*N*-[(*S*)-(1-*phenyl*)-*ethyl*]-4-(2′-*chlorophenyl*)-*azetidin*-2-*one*] (**4a**)

A white crystal (0.71 g) was obtained in 21.9% total yields by recrystallization in solvent of ethyl acetate and *n*-hexane (4∶1, *V*∶*V*). M.p. 157—158 ℃, $[\alpha]_D^{20}$ −153 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.26—7.39 (m, 9H, Ar), 5.09 (s, 2H, C**H**OH, C**H**N), 4.54 (q, *J* = 7.2 Hz, 1H, C**H**CH_3), 3.48 (brs, 1H, OH), 1.90 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.9, 140.9, 134.3, 132.4, 13 0.2, 129.7, 129.2, 129.2, 128.4, 127.3, 127.1, 77.1, 59.5, 55.0, 20.1; IR (KBr) ν: 3322, 2992, 2987, 1732 cm^{-1}; MS *m*/*z* (%): 302.0 (M + H^+, 45). Anal. calcd for $C_{17}H_{16}NO_2Cl$: C 67.66, H 5.34, N 4.64; found C 67.51, H 5.30, N 4.57.

Synthesis of [(3*R*,4*S*)-3-*hydroxy*-*N*-[(*S*)-(1-*phenyl*)-*ethyl*]-4-(4′-*chlorophenyl*)-*azetidin*-2-*one*] (**4b**)

A white crystal (2.48 g) was obtained in 76.5% total yields by recrystallization in solvent of ethyl acetate and *n*-hexane (6∶1, *V*∶*V*). M.p. 141—142.5 ℃, $[\alpha]_D^{20}$ +158 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.16—7.58 (m, 9H, Ar), 5.06 (d, *J* = 4.3 Hz, 1H, C**H**OH), 4.95 (d, *J* = 4.3 Hz, 1H, CHN), 4.55 (q, *J* = 7.2 Hz, 1H, NC**H**CH_3), 3.51 (brs, 1H, OH), 1.45 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.7, 139.7, 134.9, 134.1, 130.4, 129.2, 129.0, 128.5, 127.6, 77.3, 62.0, 52.7, 19.7; IR (KBr) ν: 3260, 2991, 2989, 1723 cm^{-1}; MS *m*/*z* (%): 302.0 (M + H^+, 48). Anal. calcd for $C_{17}H_{16}NO_2Cl$: C 67.66, H 5.34, N 4.64; found C 67.39, H 5.22, N 4.71.

Synthesis of [(3*R*,4*S*)-3-*hydroxy*-*N*-[(*S*)-(1-*phenyl*)-*ethyl*]-4-(3′-*chlorophenyl*)-*azetidin*-2-*one*] (**4c**)

A white crystal (0.60 g) was obtained in 18.5% total yields by recrystallization in solvent of ethyl acetate and *n*-hexane (4∶1, *V*∶*V*). M.p. 136—138 ℃, $[\alpha]_D^{20}$ +158 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.13—7.61 (m, 9H, Ar), 5.07 (d, *J* = 4.3 Hz, 1H, C**H**OH), 4.98 (d, *J* = 4.3 Hz, 1H, CHN), 4.53 (q, *J* = 7.2 Hz, 1H, NC**H**CH_3), 3.50 (brs, 1H, OH), 1.44 (d, 3H, *J* = 7.2 Hz, CHC**H**$_3$); IR (KBr) ν: 3257, 2992, 2989, 1723 cm^{-1}; MS *m*/*z* (%): 302.0 (M + H^+, 46). Anal. calcd for $C_{17}H_{16}NO_2Cl$: C 67.66, H 5.34, N 4.64; found C 67.47, H 5.33, N 4.79.

Synthesis of [(3*R*,4*S*)-3-*hydroxy*-*N*-[(*S*)-(1-*phenyl*)-*ethyl*]-4-(2′,4′-*dichlorophenyl*)-*azetidin*-2-*one*] (**4d**)

A white crystal (2.08 g) was obtained in 61.9% total yields by recrystallization in solvent of ethyl acetate and *n*-hexane (9∶1, *V*∶*V*). M.p. 154—157 ℃, $[\alpha]_D^{20}$ + 212 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.26—7.42 (m, 8H, Ar), 5.10 (d, J = 4.7 Hz, 1H, CHOH), 5.03 (d, J = 4.7 Hz, 1H, CHN), 4.94 (q, J = 7.2 Hz, 1H, $CHCH_3$), 1.50 (d, J = 7.2 Hz, 3H, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.9, 140.0, 135.0, 134.8, 131.9, 131.2, 129.9, 129.3, 128.6, 127.5, 127.3, 77.1, 59.2, 53.7, 19.9; IR (KBr) ν: 3258, 2990, 2900, 1718 cm^{-1}; MS *m*/*z* (%): 337.0 ($M+H^+$, 7.8). Anal. calcd for $C_{17}H_{15}NO_2Cl_2$: C 60.73, H 4.50, N 4.17; found C 60.96, H 4.41, N 3.94.

Results and discussion

Stereoselectivity

Employing chiral Schiff base via Staudinger cycloaddition reaction affords two diastereomers with 2-amide ring. The structure of **4a** has been proven by X-ray diffraction analysis (Fig. 1). The hydroxyl groups on 2-lactam and substituted phenyl groups are located at the same side, and these groups with great steric hindrance overlap with each other. 2-Position chlorine atom extends outwards maximally so as to make itself far away from hydroxyl, methyl and phenyl group. It makes hydrogen atom of chiral chain carbon overlap with hydrogen atom on ring, thus forming four-membered 3*S*,4*R* configuration ring with lower potential energy. So **4a** is proved to be (3*S*,4*R*)-3-hydroxy-*N*-[(*S*)-(1-phenyl) ethyl]-4-(2′-chlorophenyl)-azetidin-2-one. It is the first time that (3*S*,4*R*)-2-lactam compounds are obtained via Staudinger cycloaddition reaction of chiral Schiff base.

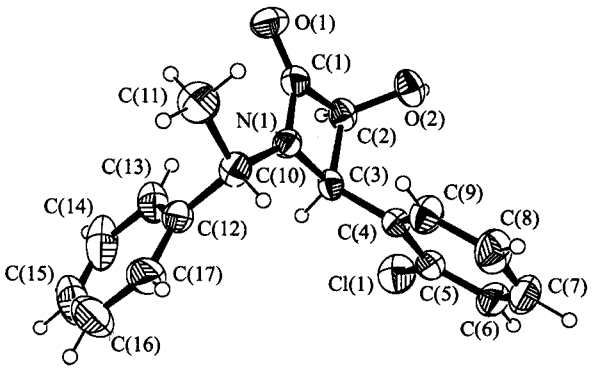


Fig. 1 X-Ray structure of [(3*S*,4*R*)-3-hydroxy-*N*-[(*S*)-(1-phenyl)ethyl]-4-(2′-chlorophenyl)-azetidin-2-one] (**4a**).

On the basis of ^1H NMR, H HCOSY, optical activity and structure of **4a**, the structures of the other 2-lactam compounds can be determined. Through analyzing the data of specific rotation, values of 2-lactam with 3*R*,4*S* configuration is more than 100 while that of 2-lactam with 3*S*, 4*R* configuration is less than − 100. According to ^1H NMR spectra, the hydrogen of NCHMe is divided into quartet due to the coupling with adjacent methyl group, which are repulsed by chlorophenyl group on 2-lactam with 3*S*,4*R* configuration. In contrast, the hydrogen of 3*R*,4*S* configuration at the same position is divided into doublet.

The ^1H NMR spectra of two-isomer mixture mentioned above show that quartet at high field belongs to 3*S*,4*R* structure isomer. According to peak area ratio of quartet and doublet, the amount ratio of 3*S*,4*R* to 3*R*,4*S* isomers can be calculated (Table 1). Similarly, **4b**, **4c** and **4d** possess 3*R*,4*S* configuration diastereoisomers with the same configuration as that of **4a**. The reaction of 2,4-dichlorophenyl Schiff base with acyl chloride can afford 3*R*,4*S* configuration product with high yield mainly due to easy separation of 3*R*,4*S* configuration product from the mixture by recrystallization.

Table 1 Stereoselectivity of cycloaddition reaction

Product	Percent (%) of 3*R*,4*S* product in mixture	Percent (%) of 3*S*,4*R* product in mixture	Yield (%) of 3*R*,4*S* product	Yield (%) of 3*S*,4*R* product
4a	42	58		21.9
4b	80	20	76.5	
4c	73	27	18.5	
4d	70	30	61.9	

Considering that rigid ring can act as controlling groups to asymmetric synthesis too, steric hindrance inevitably influences reaction to large extent. As the Table 1 shows, the position of chlorine atoms joined to benzene ring can play an important role on stereoselectivity in this reaction. From the Table, the main product of 4-chlorophenyl has 3*R*,4*S* configuration and has the highest percent in all reactions, thus 4-substituted phenyl Schiff base with bigger hindrance prefers to afford 3*R*,4*S* product, the structure of which can make substituted phenyl group far away from other phenyl groups. From the monocrystal structure of Staudinger cycloaddition products of 2-chlorophenyl Schiff base, 2-chlorine not only avoids other phenyl group but also is far away from methyl group in order to obtain the lowest potential energy, thus leading to the dominant product, 3*S*,4*R* configuration 2-lactam. As for stereoselectivity of 2,4-dichlorophenyl Schiff base, the stereoselectivity depends on corporate influence of 4- and 2-chlorines. Because the influence of 4-substituted chlorine is superior to that of 2-substituted chlorine, 3*R*, 4*S* configuration product is the main product. Although the hindrance of 3-substituent is less than that of 2-substituent, it also affects orientation of cycloaddition products and lowers selectivity of 3*R*,4*S* product.

Synthesis

The condensation of chlorophenylaldehyde and chiral amine was completed according to the reported method.[6] Considering that the amount and form of molecular sieve catalysts easily influence the reaction rate, we employed as four times catalyst amount as that of literature mentioned, and crushed catalyst particles in order to enlarge the contacting area. In this way, the reacting time was reduced from initial 2 d to 6—12 h, and the percent conversion of raw materials can achieve almost 100%.

The 2-lactam could be obtained at −20 ℃ using the similar manner reported in the literature,[6] but this low temperature reaction had some drawbacks such as inconvenient operation and low yields. For example, employing this method to synthesize **4a** the products were obtained only in 10% yield. On the basis of experimental results it was found that the reaction of acyl chloride with triethylamine to afford active intermediate was exothermal reaction and the reaction temperature almost did not influence the total yields of products. Therefore, in order to operate conveniently and increase yields, we changed the sequence of charging-up and raised the reaction temperature to −5—0 ℃, the chloroform solution of triethylamine was directly dropped into the chloroform solution of acyl chloride, then the chloroform solution of Schiff base was added to the mixture above, finally, the reaction temperature was naturally raised to room temperature. 2-Chlorophenylaldehyde with lower activity can be completely reacted only for 3—4 h with this convenient method mentioned above. Due to the viscosity of products, the recrystallization was not suitable for the separation of the products. After the hydroxyl group was freed through hydrolysis, target products were obtained through further resolution.

As for the resolution of diastereoisomers, the developing points of products appeared at the same position on thin layer plate in many developing agents leading to column chromatography unsuitable for separation. It is found that the mixture solvent of ethyl acetate and *n*-hexane with specific ratio was excellent solvent for recrystallization and the chiral 2-lactam with single configuration can be obtained with high yields. For example, 3*S*,4*R* products of **4b** and **4d** can easily be separated by recrystallization with high yields. However, 3*R*,4*S* product of **4c** was precipitated in the form of mixed crystal of diastereoisomers because of not finding ideal recrystallization solvents.

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