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Facile Synthesis of Novel Chiral Bicyclic Thioureas and Their Crystal Structures

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ABSTRACT

The novel well-defined chiral bicyclic thioureas based on enantiopure unsymmetric *cis*-2,5-disustituted pyrrolidine skeleton were firstly synthesized and fully characterized by their ^{1}H NMR, ^{13}C NMR and HRMS. Their absolute configurations were also determined by single-crystal X-ray analysis.

Keywords: Chiral Bicyclic Thiourea; *cis*-2,5-Disubstituted Pyrrolidine; X-Ray Analysis

1. Introduction

The chiral thioureas undoubtedly play an important role in asymmetric catalysis. On one hand, chiral bifunctional thioureas are excellent organocatalysts [1-5] due to their unique dual activations of both of electrophile and nucleophile, and now it is known as the term of hydrogen-bond-donor organocatalysts [6-8]. On the other hand, chiral thioureas were used as efficient ligands in Pd-catalyzed C-C bond formations [9-12] and Rh-catalyzed asymmetric reactions [13,14] and show moderate to good enantioselectiveties. Until now, most of these chiral thioureas are derived from cinchona alkaloids [15-17], 1, 2-cyclohexyldiamine [18,19], binaphthol [20,21], glucose [22,23] and *L*-proline [24-26], therefore, the exploration of preparation and application of novel chiral thioureas based on the other backbones is a challenging and interesting objective.

In our previous research work [27,28], we established a facile synthetic route to enantiopure unsymmetric *cis*-2, 5-disubstituted pyrrolidines containing hydroxyl-diamino skeleton (**Figure 1**), and herein we wish to report an efficient synthesis of novel chiral bicyclic thioureas based on the skeleton of these enantiopure pyrrolidines.

2. Results and Discussion

The chiral *cis*-2,5-disustituted pyrrolidines **1a** and **1b** were obtainned from *meso*-diethyl-2,5-dibromoadipate and (*S*)-(-)-1-phenylethylamine through six steps including cyclization, monohydrolysis, amidation, Grignard reaction, reduction and debenzylation [27]. The overall yield of six steps is about 30%.

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With the chiral *cis*-2,5-disustituted pyrrolidines **1a** and **1b** in hand, the synthesis of novel bicyclic thioureas **2** was investigated. Initially, the compound **1a** was directly used to react with thiophosgene in CH_2Cl_2 by using triethylamine (TEA) as base (**Scheme 1**), and the reaction result is complex. The chiral bicyclic thiourea **2a** was obtained only in 26% yield after purification by flash column chromatography. Because pyrrolidine **1a** possesses hydroxyl-diamino group and thiophosgene is a very active reagent, maybe thiophosgene attacks these three active reaction sites in pyrrolidine **1a** at the same time to result in some competing side reactions. In order to obtain the chiral bicyclic thiourea **2a** in high yield, the hydroxyl group in pyrrolidine **1a** should be protected.

Usually, the hydroxyl group was converted into its silyl ether in the organic protection strategy and trimethylsilyl (TMS) ether is readily stable in the presence of Et_3N, 2,6-lutidine and *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base). The chiral pyrrolidine **1a** firstly reacted with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give TMS-protected pyrrolidine **3a** in quantitative yield, and which was immediately used to react with thiophosgene to furnish TMS-protected thiourea **4a** (**Scheme 2**). In this key step, the reaction conditions were optimized and the results were shown in **Table 1**. It was found that in the presence of Hünig's base, TMS-protected thiourea **4a** was obtained in 89% crude yield by using CH_2Cl_2 as solvent. Then **4a** was deprotected by tetrabutylammonium fluoride (TBAF) in anhydrous THF to release the novel chiral bicyclic thiourea **2a** in excellent yield (94%), and **2a** was fully characterized by its ^{1}H NMR, ^{13}C NMR and HRMS.

To our satisfaction, the suitable crystals of **2a** were grown from hexane-EtOAc for X-ray diffraction analysis

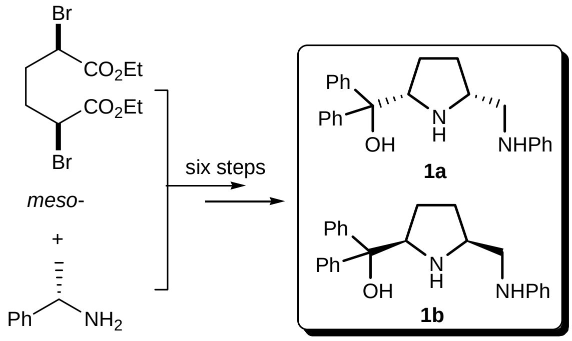
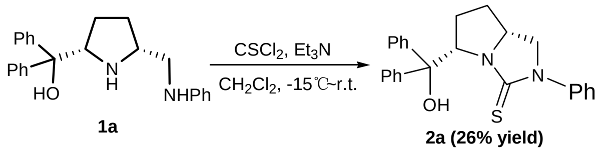
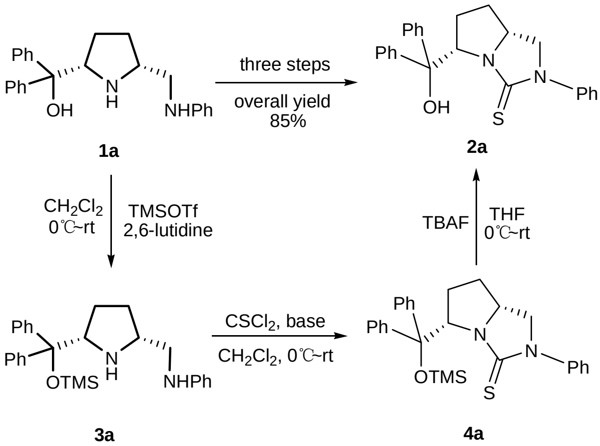


Figure 1. The synthesis of pyrrolidines 1a and 1b.



Scheme 1. The direct synthesis of 2a from 1a.



Scheme 2. The synthesis of 2a by three steps.

Table 1. The optimization of the reaction conditions of 3a with thiophosgene.

Entry	Base[a]	Solvent	Temp. [˚C]	Yield [%][b]
1	TEA	THF	r.t.	52
2	DIPEA	THF	r.t.	67
3	TEA	CH_2Cl_2	0 ~ r.t.	60
4	**DIPEA**	**CH_2Cl_2**	**0 ~ r.t.**	**89**

[a]4 eq. base was used in all entries; [b]Crude yield of product based on **3a**.

(**Figure 2**). The chiral bicyclic thiourea **2a** adopted monoclinic system and its space group is *P* 21. From the X-ray structure of **2a**, the pyrrolidine ring is obviously in *cis*-configuration, which indicates that the configurations of **1a** were retained in the synthetic process. The two five-membered rings (N1-C14-C15-C16-C17 and N1-C17-C18-N2-C19) in **2a** all adopt envelope conforma-

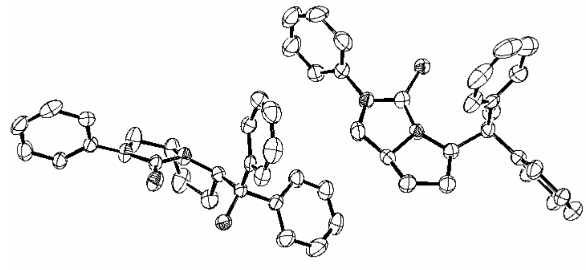


Figure 2. The X-ray structure of chiral bicyclic thiourea 2a, H atoms were omitted for clarity.

tion, and the absolute configurations of two chiral carbon atoms C14 and C17 in pyrrolidine ring are *R* and *S* respectively.

More interestingly, one cell of X-ray structure of **2a** contains two complete molecules, but the bond lengths, angles and torsion angles of these two molecules are not same. For example, two intramolecular hydrogen bonds between hydroxyl and thionyl groups were found in the X-ray structure of **2a**, but the lengths and angles of these two intramolecular hydrogen bonds are different, the length of H1---S1 (2.290 Å) is 0.039 Å shorter than H2---S2 (2.329 Å), and the angle of O2-H2---S2 (161.28˚) is 9.41˚ bigger than O1-H1---S1 (151.87˚). Some selected bond lengths, angles and X-ray crystallographic parameters of **2a** are listed in **Table 2**. The enantiomer **2b** was synthesized following the same procedure as **2a**.

The chiral thioureas **2** have several attractive features. First, the two incorporated binding sites in **2** should afford a rigid backbone for coordination with metals. Second, the steric and electronic properties of chiralthioureas **2** can be easily modified by fine-tuning the substituents. Third, the chiral thioureas **2** enjoy a good stability to air and moisture. In addition, the hydroxyl group in **2a** and **2b** can provide a hydrogen-bond donor, and the thionyl group can serve as a hydrogen-bond acceptor, so, these chiral bicyclic thioureas **2** should have potential utilities to be used as ligands or organocatalysts in asymmetric catalysis.

3. Experimental

^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solutions on a Bruker AV-300 or AV-500 spectrometer using TMS as an internal reference. Coupling constant (*J*) values are given in Hz. Mass spectra and High-resolution mass spectra were performed on a VG Micromass 7070F Mass Spectrometer with ES ionization (ESI). Crystal structure determination of compounds **2a** was carried out on a Bruker SMART CCD Single Crystal X-ray Diffractometer equipped with graphite-monochromatized $Mo_{K\alpha}$ (λ = 0.71073 Å) radiation. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares methods using *SHELX*-97. Melting points are

Table 2. Some selected crystal data, bond lengths and angles of 2a.

Parameter	Compound **2a**	Bond	Length [Å]	Bond	Angle [˚]
Empirical formula	$C_{25}H_{24}N_2O$ S	S1-C19	1.667(5)	N1-C19-S1	128.9(3)
Molecular weight	400.52	N1-C19	1.351(5)	N2-C19-S1	122.7(4)
Crystal size [mm^3]	0.31× 0.29× 0.18	N2-C19	1.356(5)	N1-C19-N2	108.4(4)
Temperature [K]	296(2)	N1-C17	1.478(6)	C19-N2-C18	112.0(4)
Crystal color	Colorless block	N2-C18	1.465(7)	N2-C18-C17	103.0(4)
Space group	*P* 21	C17-C18	1.498(5)	N1-C17-C18	103.3(4)
Crystal system	Monoclinic	N1-C14	1.464(5)	C18-C17-C16	118.1(5)
a [Å]	9.708(2)	C14-C15	1.540(6)	C17-C16-C15	105.9(4)
b [Å]	13.668(3)	C15-C16	1.524(8)	C16-C15-C14	104.1(4)
c [Å]	15.994(3)	C16-C17	1.518(8)	N1-C14-C15	102.9(3)
α [˚]	90	N2-C20	1.423(6)	C19-N1-C14	133.0(4)
β [˚]	95.284(4)	C7-C14	1.539(6)	C14-N1-C17	104.0(3)
γ [˚]	90	O1-C7	1.417(6)	C14-C7-O1	110.9(4)
U [$Å^3$]	2113.2(8)	**O1-H1---S1**	**2.290**	**O1-H1---S1**	**151.87**
μ ($Mo_{K\alpha}$) [Å]	0.71073	S2-C50	1.667(5)	N3-C50-S2	128.4(4)
D_{calc} [$Mg{\cdot}m^{-3}$]	1.259	N3-C50	1.355(6)	N4-C50-S2	124.6(4)
Z	4	N4-C50	1.358(6)	N4-C50-N3	107.1(4)
F(000)	848	N3-C42	1.472(6)	N4-C43-C42	101.1(4)
θ range [˚]	1.28 - 25.10	N4-C43	1.461(6)	C50-N3-C42	110.6(4)
Absorption coefficient [mm^{-1}]	0.172	C42-C43	1.500(7)	N3-C42-C43	100.9(4)
Completeness to θ = 25.10 [%]	99.4	N3-C39	1.473(5)	N3-C42-C41	102.8(4)
Absolute structure parameter	–0.10(10)	C39-C40	1.559(6)	C50-N3-C39	137.1(4)
Reflections collected	10761	C40-C41	1.525(7)	C42-C41-C40	105.5(4)
Unique reflections	6718	C41-C42	1.494(7)	C41-C40-C39	107.2(4)
R_{int}	0.0416	N4-C44	1.446(6)	N3-C39-C40	106.5
R_1, wR_2 [$I > 2\sigma(I)$]	0.0482, 0.1161	C32-C39	1.577(6)	C42-N3-C39	109.7(4)
R_1, wR_2 (all data)	0.0970, 0.1435	O2-C32	1.417(6)	O2-C32-C39	107.9(4)
Goodness-of-fit on F^2	1.068	**O2-H2---S2**	**2.329**	**O2-H2---S2**	**161.28**

uncorrected and expressed in degree Celsius. Optical rotations analyses were performed on a Perkin-Elmer Model 343 Polarimeter. TMSOTf was prepared from trimethylsilyl chloride and trifluoromethanesulfonic acid by Corey's procedure [29]. Solvents and reagents were purified and dried by standard methods prior to use. All reactions involving air or moisture sensitive species were performed in oven-dried glassware under inert atmosphere. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co. Ltd.

3.1. Direct Synthesis of 2a from Unprotected Pyrrolidine 1a and Thiophosgene

The chiral pyrrolidine **1a** (1.08 g, 3.0 mmol) was dissolved in 40.0 mL anhydrous CH_2Cl_2 and Et_3N (3.6 mL, 25.6 mmol) and the solution was cooled to –15˚C by ice-salt bath. Thiophosgene (0.3 mL, 3.9 mmol, CAUTION! Thiophosgene is a highly corrosive and toxic reagent) was added dropwise to the mixture and the reaction mixture was stirred at –15˚C for 45 min, then, it was continued to stir at room temperature (r.t.) overnight. The reaction was examined by thin layer chromatography (TLC). After the reaction was finished, the mixture was cooled to 0˚C and quenched by addition of 5.0 mL H_2O. The solvents were removed under reduced pressure and the residue was dissolved in 100.0 mL ethyl acetate. The organic layer was washed by water (2 × 20 mL) and brine (2 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product as yellow foam which was purified by flash column chromatography to yield 0.31 g chiral bicyclic thiourea **2a** as pale yellow powder.

3.2. Preparation of TMS-Protected Pyrrolidine 3a

To a solution of **1a** (1.44 g, 4.0 mmol) in anhydrous CH_2Cl_2 (20.0 mL) and 2,6-lutidine (5.0 mL) added dropwise TMSOTf (2.5 mL, 12.5 mmol, CAUTION! TMSOTf is a highly corrosive and moisture sensitive reagent) at 0˚C and the mixture was stirred for 1.0 h at r.t. The reaction mixture was recooled to 0˚C and quenched by addition of saturated NH_4Cl solution (2.0 mL). The mixture was diluted by 60.0 mL CH_2Cl_2 and washed by saturated NH_4Cl solution (2 × 20 mL), water (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give TMS protected pyrrolidine **3a** as brown oil in quantitative yield (1.28 g). The product was directly used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.51 - 7.12 (*m*,12H, ArH), 6.71 - 6.68 (*m*, 1H, ArH), 6.54 - 6.52 (*m*, 2H, ArH), 4.28 (*m*, 1H), 3.54 (*m*, 1H), 3.03 (m, 1H), 2.80 (m, 1H), 1.75 - 1.67 (*m*, 3H, cyclic-H), 1.14 - 1.09 (*m*, 1H, cyclic-H), –0.090 (*s*, 9H, $3CH_3Si$).

3.3. Preparation of TMS-Thiourea 4a

(5*S*,7*aR*)-Hexahydro-5-(trimethylsiloxydiphenylmethyl)-2-phenylpyrrolo(1,2-*e*)imidazole-3-thione (4a)

To a solution of **3a** (1.3 g, 3.0 mmol) in anhydrous CH_2Cl_2 (60.0 mL) and *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base, 15 mmol) added dropwise thiophosgene (0.24 mL, 3.3 mmol, CAUTION! Thiophosgene is a highly corrosive and toxic reagent) at 0˚C and the mixture was stirred for 8.0 h at r.t. The reaction was examined by TLC. After the reaction was finished, 1.0 mL H_2O was added to the reaction mixture. The organic layer was washed by water (2 × 20 mL) and brine (2 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product **4a** as yellow wax in 89% yield (1.26 g). The product was directly used in the next step without further purification. HRMS (ESI): Found $[M+1]^+$ 472.2000, Calc. for $C_{28}H_{32}N_2OSiS$: $[M+1]^+$ 472.2005; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.65 - 7.15 (*m*, 15H, ArH), 5.19 (*m*, 1H), 4.07 (*m*, 1H), 3.45 (*m*, 1H), 2.90 (*m*, 1H, cyclic-H), 2.37 (*m*, 1H, cyclic-H), 1.43 (*m*, 1H, cyclic-H), 0.28 (*m*, 1H, cyclic-H), –0.14 (*s*, 9H, $3CH_3Si$); ^{13}C NMR (500 MHz, $CDCl_3$): δ_C 179.1 (thionyl), 143.9, 141.9, 129.9, 129.8, 128.8, 127.6, 127.5, 127.3, 127.2, 127.0, 125.4, 124.7, 83.5, 64.9, 63.6, 54.9, 33.3, 25.1, 2.0 (TMS).

3.4. Preparation of Chiral Bicyclic Thiourea 2a

(5*S*,7*aR*)-Hexahydro-5-(hydroxydiphenylmethyl)-2-phenylpyrrolo(1,2-*e*)imidazole-3-thione (2a)

To a solution of **4a** (1.1 g, 2.3 mmol) in anhydrous THF (30 mL) added tetrabutylammonium fluoride (TBAF, 1.4 g) and the mixture was stirred for 2.0 h at 0˚C. The reaction was examined by TLC. After the reaction was finished, the solvents were removed under reduced pressure and the residue was dissolved in 150.0 mL ethyl acetate. The organic layer was washed by water (2 × 30 mL) and brine (2 × 30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product as yellow foam which was purified by flash column chromatography (*n*-hex/EtOAc = 5:1, V/V) to yield chiral bicyclic thiourea **2a** as pale yellow powder in 94% yield (0.87 g). mp 180˚C - 182˚C; $[\alpha]_D^{25}$ + 77.2˚ (*c* 1.0, $CHCl_3$); HRMS (ESI): Found $[M+H-H_2O]^+$ 383.1592, Calc. for $C_{25}H_{23}N_2S$: $[M+H-H_2O]^+$ 383.1582; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.58 - 7.27 (*m*, 15H, ArH), 5.03 - 5.01 (*m*, 1H), 4.23 - 4.16 (*m*, 1H), 3.73 - 3.70 (*dd*, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 3.29 - 3.24 (*dd*, 1H, J_1 = 9.0 Hz, J_2 = 3.5 Hz), 2.45 - 2.36 (*m*, 2H, cyclic-H), 1.72 - 1.67 (m, 1H, cyclic-H), 0.96 - 0.88 (m, 1H, cyclic-H). ^{13}C NMR (500 MHz, $CDCl_3$): δ_C 179.7 (thionyl), 146.5, 143.9, 141.2, 128.8, 128.6, 128.0, 127.2, 126.6, 125.4, 82.8, 65.0, 64.7, 55.7, 33.6, 25.8.

The X-ray crystallographic data for chiral bicyclicthiourea **2a** are summarized in **Table 2**.

The chiral bicyclic thiourea **2b** was prepared by the same procedure as the preparation of **2a** in 82% yield.

(5*R*,7*aS*)-Hexahydro-5-(hydroxydiphenylmethyl)-2-phenylpyrrolo(1,2-*e*)imidazole-3-thione (2b)

Overall yield 82%; pale yellow powder; mp 205˚C - 207˚C; $[\alpha]_D^{25}$ -77.0˚ (*c* 1.0, $CHCl_3$); HRMS (ESI): Found $[M+1]^+$ 401.1693, Calc. for $C_{25}H_{25}N_2OS$: $[M+1]^+$ 401.1688; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.58-7.28 (*m*, 15H, ArH), 5.03 - 5.00 (*m*, 1H), 4.22 - 4.14 (*m*, 1H), 3.73 - 3.70 (*dd*, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 3.29-3.24 (*dd*, 1H, J_1 = 8.5 Hz, J_2 = 3.5 Hz), 2.46 - 2.38 (*m*, 2H, cyclic-H), 1.71 - 1.67 (*m*, 1H, cyclic-H), 0.94 - 0.87 (*m*, 1H, cyclic-H); ^{13}C NMR (500 MHz, $CDCl_3$): δ_C 179.8 (thionyl), 146.5, 143.9, 141.0, 128.7, 128.6, 128.1, 127.2, 126.6, 125.4, 82.8, 65.1, 64.7, 55.6, 33.6, 25.8.

3.5. Supporting Information Available

The crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax +44-1223-336033. CCDC no. 694268.

4. Conclusion

In summary, we provide an efficient and practical synthetic route to the novel chiral bicyclic thioureas **2a** and **2b** based on backbone of enantiopure unsymmetric *cis*-2, 5-disubstituted pyrrolidines **1a** and **1b** by three steps in good yields, and the absolute configurations of **2a** was determined by X-ray single-crystal diffraction analysis. The applications of these novel chiral thioureas in organic synthesis were currently studied in our laboratory.

5. Acknowledgements

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