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RESEARCH ARTICLE

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Stable hemiaminals from axially chiral pyridine compounds

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Abstract

In this study, we have synthesized a series of 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol derivatives regioselectively from 2-iminothiazolidin-4-ones using $LiAlH_4$ at room temperature. Due to the presence of the restricted rotation around the N3-C_{aryl} single bond, the formation of M/P isomers was observed. The OH group of the hemiaminal was found to orient itself on the same side with pyridyl nitrogen during this restricted rotation to form an intramolecular hydrogen bond, which was demonstrated by the computational DFT study. This orientation presumably inhibited the occurrence of dehydration and stabilized the molecule.

KEYWORDS

2-iminothiazolidin-4-ol, axially chiral hemiaminal, intramolecular hydrogen bonding, pyridine compounds, stable hemiaminal

1 | INTRODUCTION

Hemiaminals are unstable and therefore unusual structural motifs. Their isolation was monitored by using nuclear magnetic resonance spectroscopy in many research,[1–3] and their transformation kinetics to related compounds were reported.[4,5] The presence of π-conjugation,[4] electron-withdrawing groups,[6] pyridine ring[7] on the structure, and intramolecular H-bonding[8–10] was found to have an important role in the stabilization of these molecules. Suni et al. obtained a stable hemiaminal as a single crystal from the condensation reaction of di-2-pyridyl ketone with 4-cyclohexyl-3-thiosemicarbazide and the X-ray diffraction result showed that the intramolecular hydrogen bonding interactions affect the stability of the molecule.[11] The intramolecular interaction between the pyridyl nitrogen group and the OH group (O—H ... N) on the structure contributing to the isolation was reported.[12] The stability of the iodohemiaminal intermediate was increased by intramolecular hydrogen bonding.[13] In the crystal structure, infinite chains of hemiaminal molecules bonded with the O—H ... N type interactions contributed to the stability of hemiaminals.[14] Subik et al. stabilized hemiaminals by attaching them to dendrimers.[15] The cross-linked hemiaminal hydrogels were found to be stable stemming from electronic effects and hydrogen bonding to the neighboring ammonium groups.[16]

Hemiaminal structure could be encountered in the structure of many biologically active natural products such as psymberin, zampanolide, and lucilactaene showing important cytotoxic activities.[17] In recent years, the hemiaminal scaffold 2-iminothiazolidin-4-ol bearing compounds have received remarkable attention because such compounds were shown to suppress lung cancer growth.[18–21]

The common pathway for the formation of hemiaminals is the condensation of amines with carbonyl compounds in which hemiaminals come about as intermediate products and easily dehydrate to the related compounds.[22] In the earlier investigations, we reported the synthesis of hemiaminals from the reduction of thiohydantoins[23] and thiazolidinones[4,5] with $LiAlH_4$ as relatively stable hemiaminals, which yielded thiazol-2-imines via spontaneous water elimination with time. The reduction of 5,5-dimethyl substituted oxazolidindiones with $NaBH_4$,[24] on the other hand, was found to yield hemiaminals that underwent ring chain ring tautomerizations.[25]

In the present study, we aimed to synthesize hemiaminals starting from axially chiral pyridine compounds, which stabilize themselves by making intramolecular H-bonds.

2 | MATERIALS AND METHODS

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra of all compounds were recorded on a Varian-Mercury VX-400 MHz-BB. IR spectra were recorded on Thermo Nicolet 380 FT-IR spectrometer. Melting points were determined on the Electrothermal 9100 melting point apparatus. Liquid chromatography analyses with an ultraviolet (UV) detector ($\lambda = 254$ nm) were performed using the CHIRALPAK IB column (particle size, 5 μm; column size, 250 × 4.6 mm^2). All reagents and solvents were obtained commercially (Aldrich, Merck) and used without further purification.

2.1 | A general procedure for the preparation of Compounds 3 and 4

The appropriate *N*,*N*′-diarylthiourea and 2-bromo-propionic acid were refluxed for 4 h in absolute ethanol in the presence of sodium acetate. At the end of this period, the excess ethanol was distilled out, and the reaction mixture was poured into cold water. Then a precipitate was obtained, collected, and washed several times with hot water to remove unreacted 2-bromo-propionic acid and sodium acetate.[26]

2.1.1 | 5-methyl-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one (3)

This compound was synthesized according to the general procedure using 1,3-di(pyridin-2-yl)thiourea 1.15 g (5 mmol) and 2-bromo-propionic acid: 0.76 g (5 mmol) in 30 mL ethanol in the presence of sodium acetate (0.49 g, 6 mmol). Yield: 0.71 g (50%), mp: 152–154 C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, 1H, ArH, $J = 3.6$ Hz), 8.46 (d, 1H, ArH, $J = 3.6$ Hz), 7.94 (td, 1H, ArH, $J = 7.8$ Hz and $J = 1.8$ Hz), 7.65 (td, 1H, ArH, $J = 7.8$ Hz and $J = 1.8$ Hz), 7.50–7.40 (m, 2H, ArH), 7.06 (td, 1H, ArH, $J = 7.8$ Hz and $J = 1.8$ Hz), 7.00 (d, 1H, ArH, $J = 7.8$ Hz), 4.20 (q, 1H, CH at C-5, $J = 7.2$ Hz), 1.80 (d, 3H, CH_3 at C-5, $J = 7.2$ Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 157.9, 157.2, 149.9, 148.9, 146.2, 138.6, 138.3, 124.3, 124.1, 121.1, 120.1, 42.7, 18.8 ppm. ATR-FTIR: 1715, 1597 cm^{-1}.

2.1.2 | 5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-one (4)

This compound was synthesized according to the general procedure using 1,3-bis(3-methylpyridin-2-yl)thiourea 1.29 g (5 mmol) and 2-bromo-propionic acid: 0.76 g (5 mmol) in 30 mL ethanol in the presence of sodium acetate (0.49 g, 6 mmol). Yield: 0.82 g (52%), mp: 130–132 C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, 1H, ArH $J = 3.6$ Hz), 8.20 (d, 1H, ArH, $J = 3.6$ Hz), 7.66 (d, 1H, ArH, $J = 7.2$ Hz), 7.38 (d, 1H, ArH, $J = 7.2$ Hz), 7.28 (dd, 1H, ArH, $J = 7.2$ and $J = 4.8$ Hz), 6.90 (t, 1H, ArH, J = 3.6 Hz), 4.12 (q, 1H, CH at C-5, $J = 7.2$ Hz), 2.23 (s, 3H, CH_3 on N-3 aryl group), 1.88 (s, 3H, CH_3 on iminoaryl group), 1.72 (d, 3H, CH_3 at C-5 $J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 156.0, 148.2, 147.4, 143.2, 139.9, 132.4, 129.6, 124.7, 120.2, 42.9, 42.8, 19.2, 18.9, 17.2, 17.0, 16.8 ppm. ATR-FTIR: 1722, 1604 cm^{-1}.

2.2 | A general procedure for the reduction of 2-imino-thiazolidine-4-ones to their hemiaminal derivatives in the presence of $LiAlH_4$

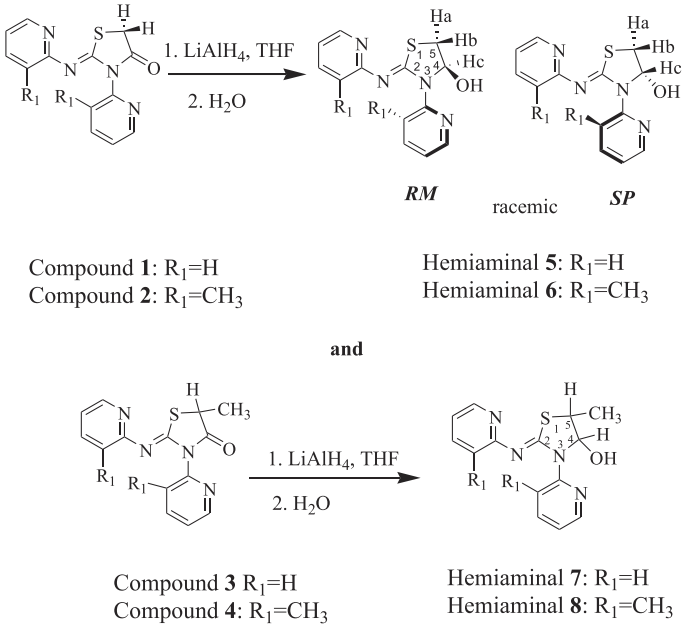
The appropriate amount of 2-imino-thiazolidine-4-one was dissolved in THF, and 1.5 equivalent $LiAlH_4$ was added to the mixture. The reaction mixture was stirred at room temperature for 5 min. At the end of the period, water was added to quench the reaction. The mixture was extracted with ethyl acetate and dried with $CaCI_2$, and the solvent was evaporated.

2.2.1 | (±)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (5)

This compound was synthesized according to the general procedure using Compound **1** (0.1 g, 0.37 mmol), $LiAlH_4$ (0.021 g, 0.56 mmol) and 10 mL THF. Yield: 0.065 g (65%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, 1H, ArH, $J = 4.0$ Hz), 8.34 (m, 2H, ArH), 7.80 (m, 1H, ArH), 7.71 (m, 1H, ArH), 7.11 (m, 2H, ArH), 7.05 (m, 1H, ArH), 6.24 (d, 1H, CH at C-4, $J = 5.6$ Hz), 5.52 (br, s, 1H, OH), 3.52 (dd, 1H, CH at C-5, $J = 12.0$ Hz and $J = 5.6$ Hz), 3.27 (d, 1H, CH at C-5, $J = 12.0$ Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 156.1, 150.3, 148.1, 138.6, 125.6, 122.4, 119.5, 117.3, 104.8, 85.4, 34.0 ppm. ATR-FTIR: 3331, 1654 cm^{-1}. HRMS (TOF MS ES+): calculated for $C_{13}H_{12}N_4OS$: 273.0700; found: 273.0680.

2.2.2 | (±)-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-ol (**6**)

This compound was synthesized according to the general procedure using Compound **2** (0.1 g, 0.34 mmol), $LiAlH_4$ (0.019 g, 0.50 mmol) and 10 mL THF. Yield: 0.052 g (51%), pale yellow crystal, mp: 168–170 C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.2 (d, 2H, ArH, $J = 2.8$ Hz), 7.61 (d, 1H, ArH, $J = 7.2$ Hz), 7.35 (d, 1H, ArH, $J = 6.8$ Hz), 7.18 (dd, 1H, ArH, $J = 4.8$ Hz and $J = 7.2$ Hz), 6.83 (dd, 1H, ArH, $J = 4.8$ Hz and $J = 7.2$ Hz), 6.22 (br, s, 1H, OH), 5.80 (d, 1H, CH at C-4, $J = 4.8$ Hz), 3.49 (dd, 1H, CH at C-5, $J = 11.6$ Hz and $J = 4.8$ Hz), 3.21 (d, 1H, CH at C-5, $J = 11.6$ Hz), 2.30 (s, 3H, CH_3 on N-3 aryl group), 2.00 (d, 3H, CH_3 on iminoaryl group) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 154.1, 145.0, 144.2, 139.9, 138.3, 131.6, 128.3, 122.5, 119.1, 83.9, 36.1, 18.8, 17.4 ppm. ATR-FTIR: 3338, 1575 cm^{-1}. HRMS (TOF MS ES+): calculated for $C_{15}H_{16}N_4OS$: 301.1120; found: 301.1123.



SCHEME 1 Synthesis of the stable hemiaminals from axially chiral pyridine compounds.

2.2.3 | (±)-5-methyl-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (**7**)

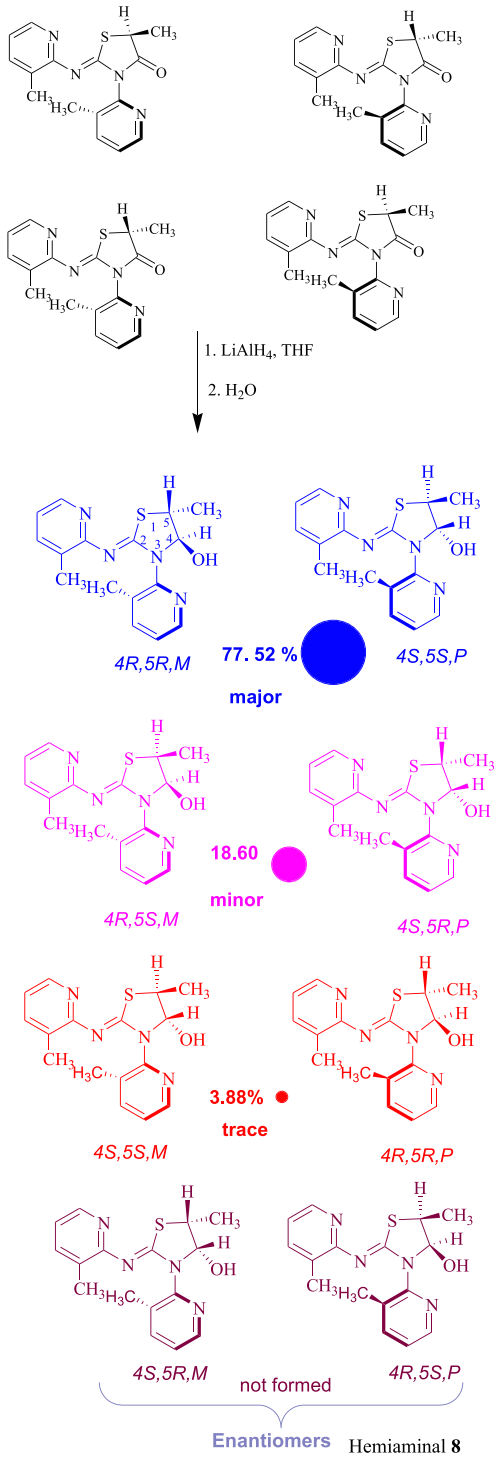
This compound was synthesized according to the general procedure using Compound **3** (0.1 g, 0.35 mmol), $LiAlH_4$ (0.02 g, 0.53 mmol) and 10 mL THF. Yield: 0.043 g (43%), yellow colored solid, mp: 64–66 C. ^1H NMR (400 MHz, $CDCl_3$): for major isomer δ 8.42–6.34 (m, 8H, ArH), 5.82 (d, 1H, CH at C-4, $J = 0.8$ Hz), 5.12 (br, 1H, OH), 3.56 (qd, 1H, CH at C-5, $J = 0.8$ Hz and $J = 7.2$ Hz), 1.48 (d, 3H, CH_3, $J = 7.2$ Hz) ppm and for minor isomer δ 8.43–6.72 (m, 8H, ArH), 5.96 (d, 1H, CH at C-4, $J = 5.2$ Hz), 5.29 (br, 1H, OH), 3.86 (qd, 1H, CH at C-5, $J = 5.2$ Hz and $J = 7.2$ Hz), 1.54 (d, 3H, CH_3, $J = 6.8$ Hz ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 159.3, 157.7, 153.2, 153.0, 147.3, 137.6, 137.6, 137.5, 137.4, 119.6, 119.5, 118.9, 118.8, 113.4, 109.4, 89.7, 85.1, 43.3, 41.9, 21.2, 13.0 ppm. ATR-FTIR: 3342, 1589 cm^{-1}. HRMS (TOF MS ES+): calculated for $C_{14}H_{14}N_4OS$: 287.0960; found: 287.0967.

2.2.4 | (±)-5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-ol (**8**)

This compound was synthesized according to the general procedure using Compound **4** (0.1 g, 0.32 mmol), $LiAlH_4$ (0.018 g, 0.48 mmol) and 10 mL THF. Yield: 0,038 g (38%), yellow colored solid, mp: 112–115°C. ^1H NMR (400 MHz, $CDCl_3$): for major isomer δ 8.06–6.60 (m, 6H, ArH), 6.27 (br s, 1H, OH), 5.26 (s, 1H, CH at C-4), 3.50 (q, 1H, CH at C-5, $J = 7.2$ Hz), 2.21 (s, 3H, CH_3 on N-3 aryl group), 2.09 (s, 3H, CH_3 on iminoaryl group), 1.21 (d, 3H, CH_3 at C-5, $J = 7.2$ Hz) ppm and for minor isomer δ 8.06–6.60 (m, 6H, ArH), 6.27 (br s, 1H, OH), 5.26 (s, 1H, CH at C-4), 3.60 (dq, 1H, CH at C_5, $J = 6.8$ Hz and $J = 11.2$ Hz), 2.29 (s, 3H, CH_3 on N-3 aryl group), 2.09 (s, 3H, CH_3 on iminoaryl group), 1.54 (d, 3H, CH_3 at C-5, $J = 6.8$ Hz) ppm and for trace isomer δ 8.06–6.60 (m, 6H, ArH), 6.27 (br s, 1H, OH), 4.82 (s, 1H, CH at C-4), 3.94 (dq, 1H, CH at C_5, $J = 6.8$ Hz and $J = 11.2$ Hz), 2.51 (s, 3H, CH_3 on N-3 aryl group), 2.31 (s, 3H, CH_3 on iminoaryl group), 1.33 (d, 3H, CH_3 at C-5, $J = 6.8$ Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 156.8, 146.4, 144.9, 143.8, 139.6, 138.1, 131.3, 128.0, 123.5, 122.2, 120.4, 118.7, 117.2, 116.4, 113.3, 89.7, 85.7, 45.2, 44.0, 20.9, 18.4, 18.2, 17.2 ppm. ATR-FTIR: 3358, 1599 cm^{-1}. HRMS (TOF MS ES+): calculated for $C_{16}H_{18}N_4OS$: 315.1283; found: 315.1280.

2.3 | Computational procedure

The stereoisomers of Hemiaminal **6** (*RM*, *RP* and their enantiomers, Scheme 1) and hemiaminal **8** ((4*R*,5*R*,*M*), (4*R*,5*S*,*M*), (4*S*,5*S*,*M*), (4*S*,5*R*,*M*) and their enantiomers, Scheme 2) were prepared in Spartan 16.[27] First, all possible conformations of Hemiaminals **6** and **8** were determined for each stereoisomer using the conformer distribution module with molecular mechanics (MMFF)



SCHEME 2 The expected eight isomers for Hemiaminal **8** (the different colored balls under the molecules) represent the enantiomeric pairs on the partial ^{1}H NMR in Figure 3.

method. These structures were optimized with a much higher level of theory utilizing density functional theory with M06-2X/6-31G** method[28,29] in the gas phase based on its performance in previous studies.[30–33] Then, low energy conformations of all isomers were further

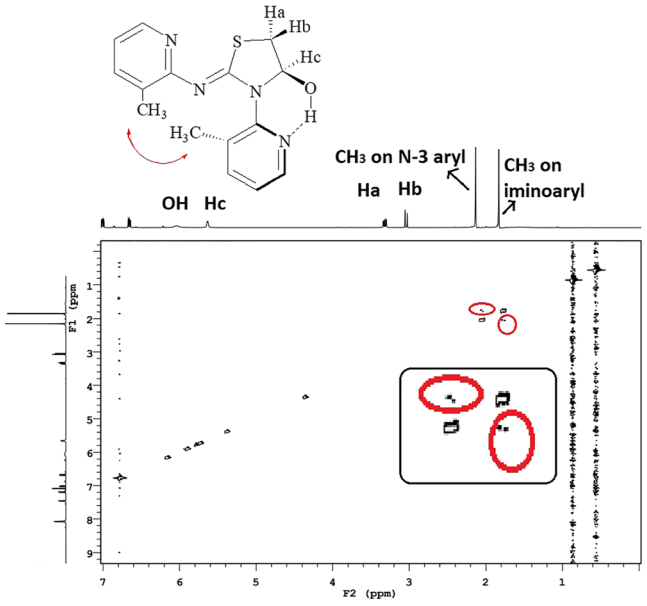


FIGURE 1 The NOESY spectrum of Hemiaminal **6** shows the cross peak between the methyl groups.

optimized with the same method in chloroform using PCM solvent model[34] in Gaussian 09.[35] Gibbs free energies were obtained from frequency calculations at 298 K and 1 atm. The percent contribution of each conformation was calculated by Boltzmann probability distribution as described by Ozalp et al.[36]

3 | RESULTS AND DISCUSSION

3.1 | Synthesis of the axially chiral stable hemiaminals and identification of their isomers by ^{1}H NMR

We synthesized a series of stable 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (5-6) and 5-methyl-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (7-8) derivatives (hemiaminals) regioselectively from the reduction of 2-iminothiazolidin-4-one derivatives with $LiAlH_4$ (Scheme 1). The identification of the synthesized compounds was done by NMR analyses.

The Hemiaminals **5–8** obtained from axially chiral pyridine compounds[26] did not undergo an elimination reaction to form the corresponding imines (Scheme 1). We followed their stability in solvent-free media and in $CDCl_3$ and found that they are stable in both. When we reduced the axially chiral Compound **2** using $LiAlH_4$ in THF at room temperature, Hemiaminal **6** was obtained. Hemiaminal **6**, in addition to its chiral axis, the N3-C_{aryl} single bond, also has a chiral center at C-4. Thus, it would, in principle, be expected to exist in four

stereoisomers as two diastereomeric pairs: *RM/SP* and *RP/SM*. However, in the ^{1}H NMR spectrum of the Hemiaminal **6**, only one set of signals was observed, indicating the presence of only one of these diastereomeric pairs. A detailed analysis of the ^{1}H NMR spectrum of Hemiaminal **6** is important because the determination of the stereochemistry of the synthesized molecules was done according to its ^{1}H NMR spectrum. In ^{1}H-NMR, the diastereotopic protons H_a and H_b at C-5 resonate at different frequencies. They couple with each other, but H_b does not couple with H_c (Scheme 1, Figure 1). The H_c proton at C-4 gave a doublet at δ 5.80 ppm by coupling with H_a at C-5 ($^3JH_aH_c = 4.8$ Hz), which is cis to it; however, not with H_b that is trans to it ($^3JH_bH_c = \sim 0$ Hz) (Figure 1). The H_a proton appeared at δ 3.49 ppm (dd), giving a geminal coupling with H_b ($^2JH_aH_b = 11.6$ Hz) and a vicinal coupling with H_c ($^3JH_aH_c = 4.8$ Hz). The H_b proton showed coupling with only the H_a ($^2JH_aH_b = 11.6$ Hz and $^3JH_bH_c = \sim 0$ Hz) and appeared as a doublet at δ 3.21 ppm[5]. The formation of an intramolecular hydrogen bond between the N-3 pyridyl nitrogen and the hemiaminal OH (Figure 1) was also deduced from the ^{1}H NMR spectrum, where the OH signal was observed to shift to more downfield (from 2.40–3.00 ppm[23] to 6.22 ppm). Previously, our research group observed the OH signal of a hemiaminal derivative at 6.60 ppm, where there was an intermolecular hydrogen bonding between the solvent (DMF) and the OH group.[4] The oxygen atoms of aprotic and polar solvents are very often involved in strong hydrogen bonding interactions with the acidic protons of solute molecules (usually protons of —OH, —NH, or —SH moieties). In such bonding, the solvent withdraws the electron density from the hydrogen atoms involved; therefore, these proton signals are shifted downfield.[37] In the present study, because we used $CDCl_3$ as a solvent, the formation of a hydrogen bond with the solvent was not expected. We explained the appearance of the OH signal in more downfield due to the formation of an intramolecular hydrogen bonding. To elucidate the stereochemistry of the hemiaminals, a 2D-NOESY spectrum was taken in $CDCl_3$ (Figure 1). A cross peak between the CH_3 groups on the N-3 aryl and iminoaryl groups was observed (Figure 1). Therefore, the OH group is expected to prefer to be on the same side with the N-3 pyridyl nitrogen probably because of the possibility for an

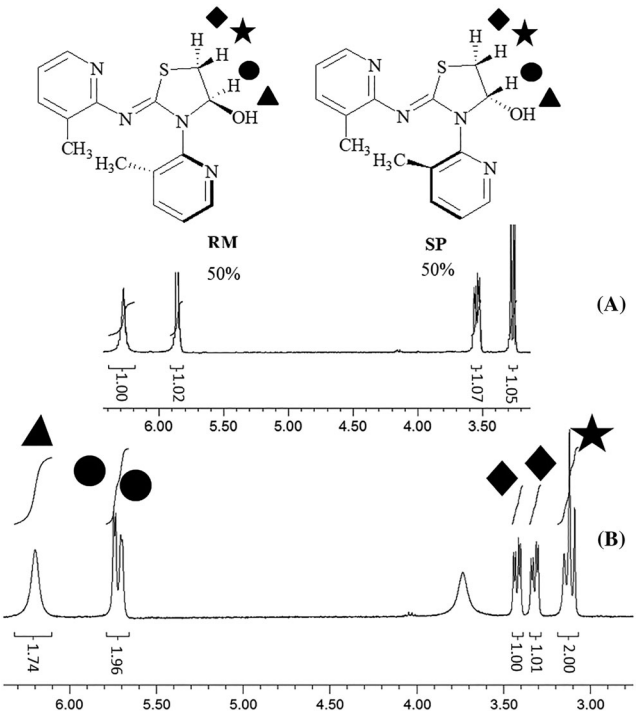


FIGURE 2 The partial ^{1}H NMR spectra of Hemiaminal **6** in the absence of chiral auxiliary (A) and the presence of chiral auxiliary (*R*)-TFAE (1:1) show the enantiomer ratio (racemic) (B).

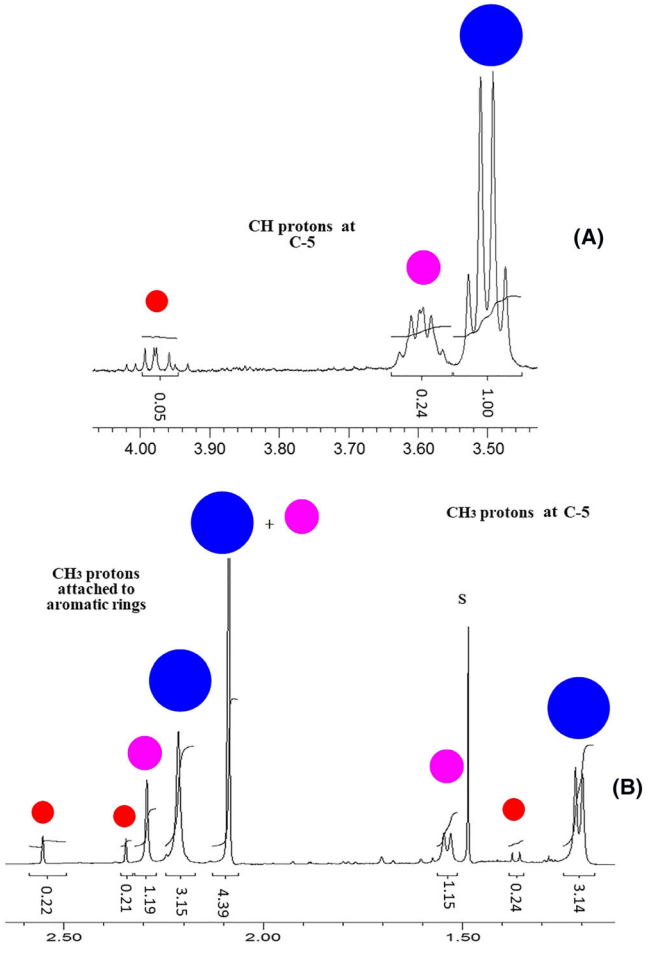


FIGURE 3 Partial ^{1}H NMR spectrum of Hemiaminal **8** shows the quartet for CH proton at C-5 (A) and the CH_3 groups at C-5 and attached to pyridine rings (B).

intramolecular H-bond formation (Figures 1 and 2). In the light of the 2D-NOESY spectrum, the stereochemistry of Hemiaminal **6** was assigned as *RM/SP*. The racemic nature of Hemiaminal **6** was shown in ^{1}H NMR in the presence of 1 equivalent of chiral auxiliary (*R*)-TFAE (Figure 2). The ^{13}C NMR spectrum of Hemiaminal **6** showed a signal for carbon at the C-4 position on which the OH group was attached at 83.9 ppm.

The synthesis of Compound **4** was carried out using 1,3-bis(3-methylpyridin-2-yl)thiourea and 2-bromopropionic acid in ethanol. The detection of the isomers of Compound **4** was done on HPLC on chiralpak IB. For the analysis, *n*-Hexane/2-Propanol (85/15, flow rate: 0.6 mL/min) mixture was used as a mobile solvent. Under these conditions, the diastereomeric percent ratio of the isomers was found as 84.1% and 15.9% (*RM/SP:SM/RP*). When we reduced this isomeric mixture (*RM/SP:SM/RP*) of Compound **4** to its Hemiaminal **8**, the formation of eight isomers could be expected due to the presence of the chiral center at C-5, the N3-$C_{(aryl)}$ chiral axis and the newly formed chiral center at C-4 (Scheme 2). However, the ^{1}H NMR spectrum of Hemiaminal **8** showed three sets of peaks for three enantiomeric pairs (Figure 3). The assignment of major, minor and trace isomers was done according to the orientation of the OH and CH_3 groups on the N-3 aryl. The larger groups OH at C-4 and CH_3 group at C-5 stayed anti to each other, and the OH group preferred to make an H-bond with the nitrogen atom of the pyridyl ring at N-3. Consequently, (4*R*,5*R*,*M*/4*S*,5*S*,*P*) enantiomeric pair was assigned as the major and the (4*R*,5*S*,*M*/4*S*,5*R*,*P*) enantiomeric pair as the minor product. The ratio of the isomers (major:minor:trace) was determined as 77.52:18.60:3.88 from the ^{1}H NMR spectrum. The CH protons of major, minor, and trace isomers at C-5 gave a quartet (at 3.50 ppm) and doublet of the quartet (at 3.60 and 3.97 ppm [trace]) (Figure 3A). The signals for CH_3 protons at C-5, CH_3 groups on iminoaryl and N-3 aryl groups were shown in Figure 3B. The CH protons of major and minor isomers at C-4 coincided and gave a singlet at 5.26 ppm and a singlet at 4.82 ppm for trace isomers. In the ^{1}H NMR spectrum of Hemiaminal **8**, OH signals of isomers coincided with each other and appeared as a broad signal at 6.27 ppm.

The ^{13}C NMR signals of C-4 carbon of the major and minor isomers of Hemiaminal **8** appeared at 89.7 and 85.7 ppm, and C-5 carbons of the major and minor isomers were observed at 45.2 and 44.0 ppm.

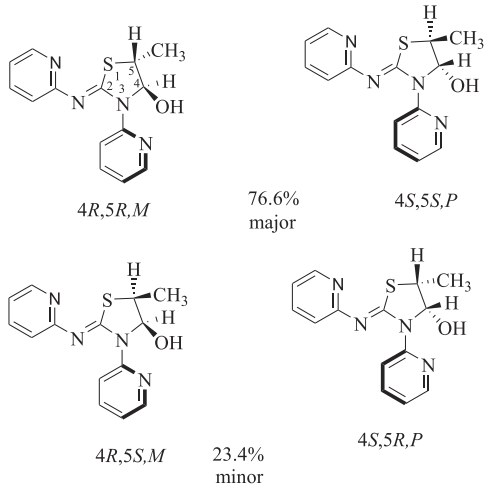


FIGURE 4 The chemical structures of major and minor isomers of Hemiaminal **7**.

TABLE 1 Calculated Gibbs free energies, Boltzman percentages,[a] and experimental percentages for all stereoisomers of Hemiaminal **6**.

Isomers and conformations[b]		Energy (au)	Calculated %	Total %	Experimental %
RM	c1	−1273.056709	49.03		
	c2	−1273.050811	0.10	49.13	50
SP	c1	−1273.056709	49.03		
	c2	−1273.050811	0.10	49.13	50
RP	c1	−1273.052452	0.54		
	c2	−1273.051953	0.32		
	c3	−1273.049096	0.01	0.87	Not formed
SM	c1	−1273.052452	0.54		
	c2	−1273.051953	0.32		
	c3	−1273.049096	0.01	0.87	Not formed

[a]The conformations contributing more than 0.01% were included in the table.

[b]c1, c2, and c3 stand for the most stable, second most stable, and third most stable conformations.

TABLE 2 Calculated Gibbs free energies, Boltzman percentages,[a] and experimental percentages for all stereoisomers of Hemiaminal **8**.

Isomers	Conformations[b]	Energy (au)	Calculated %	Total %	Experimental %
4*R*,5*R*,*M*	c1	−1312.328874	35.82		
	c2	−1312.322815	0.06		
	c3	−1312.322369	0.04		
	c4	−1312.321002	0.01		
		4*R*,5*R*,*M* total	35.92		
4S,*5S*,*P*	c1	−1312.328875	35.86		
	c2	−1312.322815	0.06		
	c3	−1312.321870	0.02		
	c4	−1312.320989	0.01		
		4*S*,5*S*,P total	35.95	71.87	77.52 (Major)
4*R*,5*S*,*M*	c1	−1312.327953	13.51		
	c2	−1312.322462	0.04		
	c3	−1312.320872	0.01		
		4*R*,5*S*,*M* total	13.56		
4*S*,5*R*,*P*	c1	−1312.327952	13.49		
	c2	−1312.322462	0.04		
	c3	−1312.320871	0.01		
		4*S*,5*R*,*M* total	13.54	27.10	18.60 (Minor)
4*S*,5*S*,*M*	c1	−1312.324181	0.25		
	c2	−1312.323374	0.11		
		4*S*,5*S*,*M* total	0.36		
4*R*,5*R*,*P*	c1	−1312.324181	0.25		
	c2	−1312.323364	0.10		
		4*R*,5*R*,*P* total	0.35	0.71	3.88 (Trace)
4*S*,5*R*,*M*	c1	−1312.323277	0.10		
	c2	−1312.322569	0.05		
	c3	−1312.321644	0.02		
		4*S*,5*R*,*M* total	0.16		
4*R*,5*S*,*P*	c1	−1312.323277	0.10		
	c2	−1312.322569	0.05		
	c3	−1312.321644	0.02		
		4*R*,5*S*,*P* total	0.16	0.32	Not formed

[a]The conformations contributing more than 0.01% were included in the table.
[b]c1, c2, and c3 stand for the most stable, second most stable, and third most stable conformations.

Compound **3** was obtained from the reaction of 1,3-di(pyridin-2-yl)thiourea and 2-bromo-propionic acid in ethanol. Different HPLC peaks for *P* and *M* isomers were not observed due to the fast rotation around the N3-$C_{(aryl)}$ single bond for Compound **3**. We have started a racemic mixture of *RM* and *SP* enantiomers. The detection of enantiomers was done on HPLC on chiralpak IB (*n*-Hexane/2-Propanol [70/30, flow rate: 0.6 mL/min]). When Compound **3** was reduced to Hemiaminal **7**, the formation of eight isomers could be expected due to the presence of three chiral elements (two chiral centers and a chiral axis) as in Hemiaminal **8**. However, due to the fast rotation around the chiral axis, only two sets of peaks were observed in the ^{1}H NMR spectrum of Hemiaminal **7** belonging to (4*R*,5*R*,*M*/4*S*,5*S*,*P*) enantiomeric pair as the major isomer and (4*R*,5*S*,*M*/4*S*,5*R*,*P*) enantiomeric pair as the minor one similar to the case in Hemiaminal **8** (Figure 4). The diastereomeric ratio of the major to minor isomers was determined as 77:23 according to ^{1}H NMR spectrum of Hemiaminal **7**.

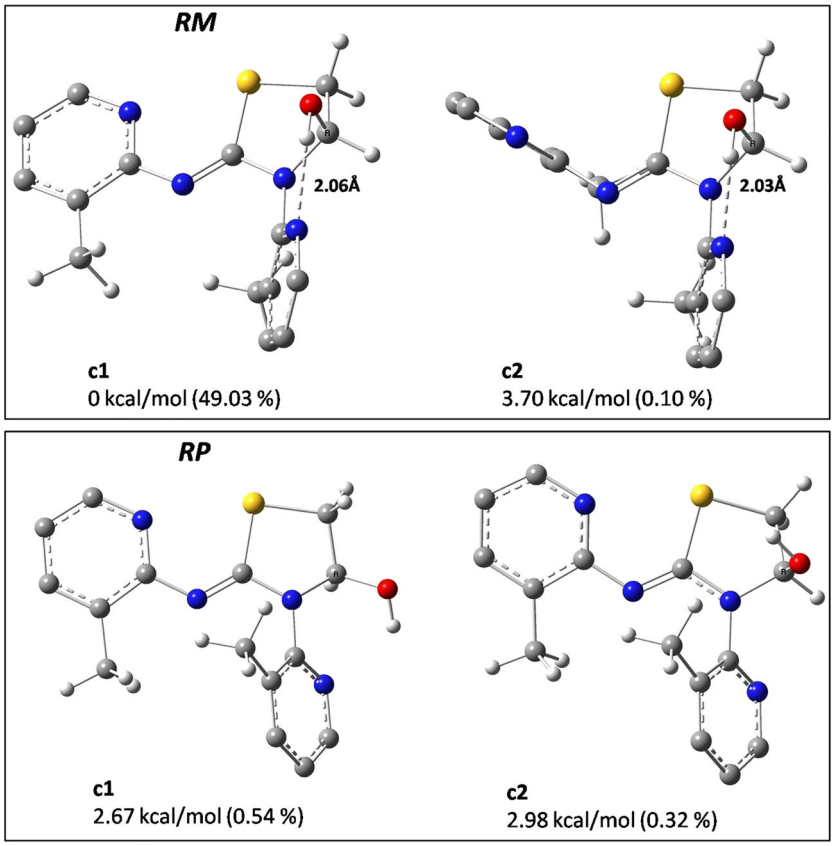


FIGURE 5 Relative Gibbs free energies (kcal/mol), percentages and 3-D view of the first two lowest energy conformations (c1, c2) of *RM* and *RP* diastereomers for Hemiaminal **6** obtained from M06-2X/6-31G(d,p) optimizations in chloroform solvent.

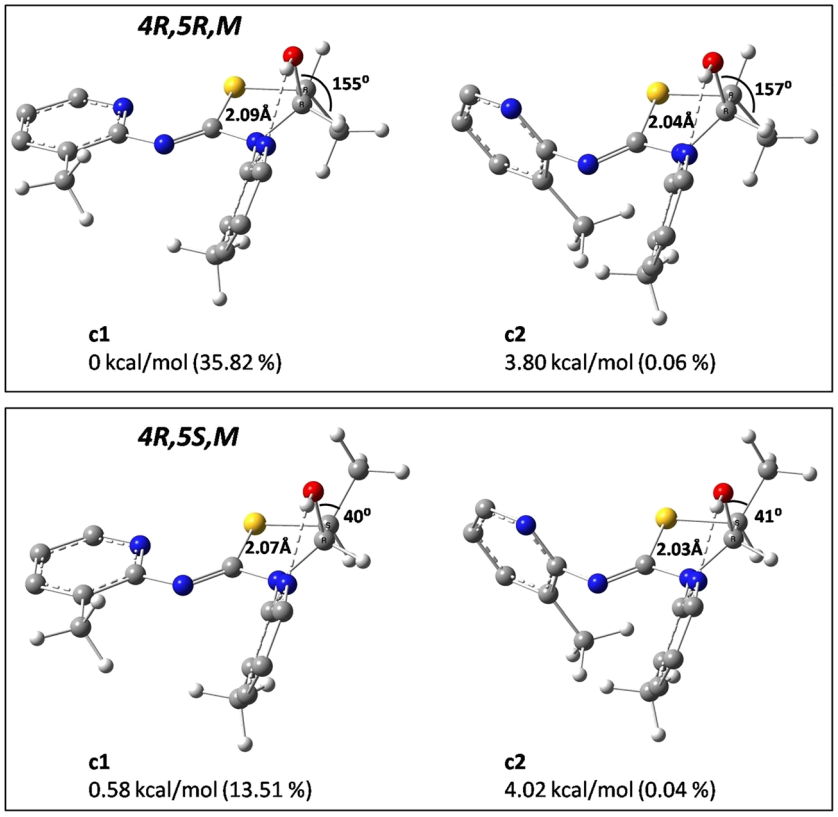


FIGURE 6 Relative Gibbs free energies (kcal/mol), percentages and 3-D view of the first two lowest energy conformations (c1, c2) of Hemiaminal **8** major (4*R*,5*R*,*M*) and minor (4*R*,5*S*,*M*) diastereomers obtained from M06-2X/6-31G(d,p) optimizations in chloroform solvent.

3.2 | Computational study

In order to provide insight into the experimental observations we conducted a detailed conformational analysis for all stereoisomers of the representative Hemiaminals **6** and **8**. For each diastereomer of Hemiaminals **6** and **8**, about eight and 40 conformations were generated, respectively, by Spartan.[27] Please note that only the low energy conformations that contribute to the percent distribution are listed in Tables 1 and 2. Table 1 displays Gibbs free energies of all stereoisomers for Hemiaminal **6** and their percent contributions based on Boltzman distribution. The ratio of *RM* and *SP* enantiomers is 49.13:49.13, whereas *RP* and *SM* pair ratio is 0.87:0.87. It is evident that *RM* and *SP* enantiomeric pair is almost the only product for Hemiaminal **6**. These results are in very good agreement with the experimental data where *RM:SP* ratio is 50:50. The first two most stable conformations of *RM* and its diastereomer *RP* are shown in Figure 5. (The conformations of their enantiomers *SP* and *SM* are not shown because they exhibit the same conformations as *RM* and *RP*). Both *RM* conformations (c1 and c2) display intramolecular hydrogen bonds (with interaction distances 2.06 Å and 2.03 Å, respectively) between OH group and N-3 pyridyl nitrogen, forming a six-membered ring. On the other hand, *RP* conformations do not have hydrogen bonds with almost no contribution to percent distribution as expected. Accordingly, the most important factor for the formation of *RM* and *SP* enantiomeric pair is the intramolecular hydrogen bond formation in these hemiaminal structures.

Calculated Gibbs free energies and the percent contributions for Hemiaminal **8**, (4*R*,5*R*,*M*), (4*R*,5*S*,*M*), (4*S*,5*S*,*M*), (4*S*,5*R*,*M*) isomers and their enantiomers are given in Table 2. The total diastereomeric percent ratio was found to be 71.87: 27.10: 0.71: 0.32, respectively, which is in agreement with the experimental data 77.52: 18.60: 3.88: 0.0 (Table 2). The two most stable conformations of major (4*R*,5*R*,*M*) and minor (4*R*,5*S*,*M*) diastereomers are shown in Figure 6. Their enantiomers are not shown because they exhibit the same interactions as in 4*R*,5*R*,*M* and 4*R*,5*S*,*M* isomers. In both c1 and c2 conformations of major and minor, there appears to be a hydrogen bond between OH and N-3 facing on the same side, and the lone pair of N-3 is properly directed toward the OH proton, which leads to about 2 Å interaction distance. The only difference in the low energy conformations of these diastereomers is the position of the methyl group at the C-5 chiral center. The dihedral angles between OH and CH_3 groups are 155° and 157° for the 4*R*,5*R*,*M* conformations, which are closer to anti conformations. However, for the conformations of minor diastereomer (4*R*,5*S*,*M*), the same dihedral angles are remarkably smaller (40° and 41°) because both OH and CH_3 groups are directed to the same side leading to torsional repulsions due to

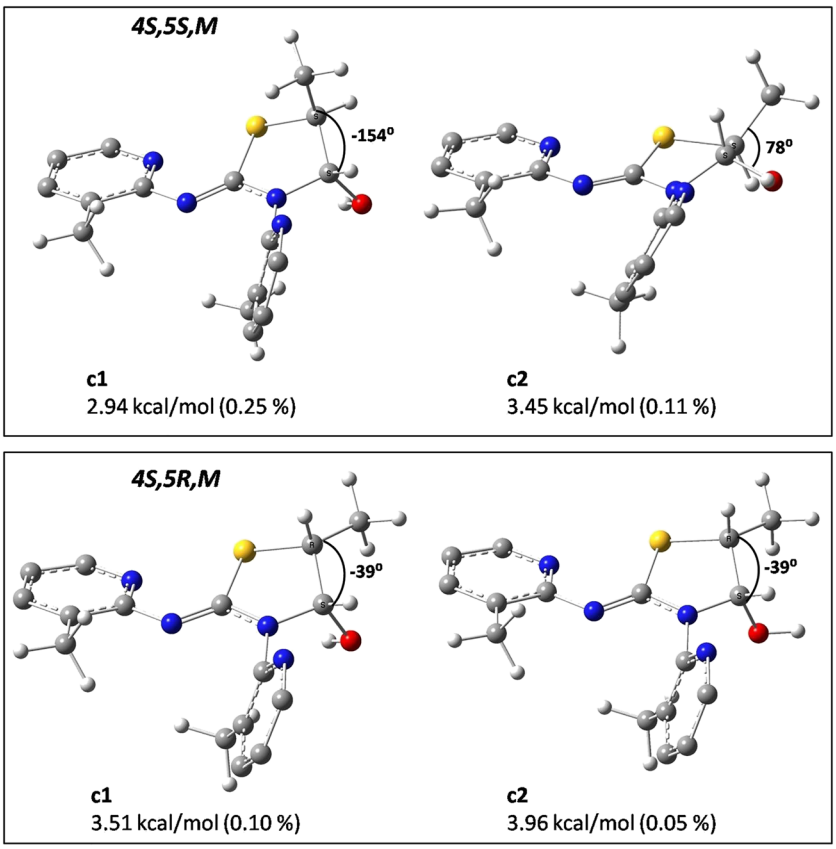


FIGURE 7 Relative Gibbs free energies (kcal/mol), percentages and 3-D view of the first two lowest energy conformations (c1, c2) of Hemiaminal **8** 4*S*,5*S*,*M* and 4*S*,5*R*,*M* diastereomers obtained from M06-2X/6-31G(d,p) optimizations in chloroform solvent. All energies are relative to the most stable conformation of 4*R*,5*R*,*M* c1 in Figure 6.

smaller gauche angle. This syn interaction results in 0.58 and 0.22 kcal/mol increase in the Gibbs free energy differences between the conformations of major and minor isomers, respectively. Because the percent contributions of c2 conformations are remarkably small, the 0.58 kcal/mol rise in the energy of c1 conformation is the main factor responsible for the smaller percentage of the minor isomer with respect to the major one, which originates from the syn interaction between OH and CH_3 groups.

The most stable conformations of the remaining diastereomers 4*S*,5*S*,*M* and 4*S*,5*R*,*M* are shown in Figure 7. These structures do not exhibit a hydrogen bond since OH and N-3 are on opposite sides, and N-3 lone pair is not properly oriented. As a result, their contribution is calculated to be negligibly small (0.7% and 0.3%, respectively) and follows the same order as in experimentally determined percentages (Table 2). Similar to the case of major and minor diastereomers, the smaller percent contribution of *4S*,*5R*,*M* with respect to 4*S*,5*S*,*M* is mainly due to the smaller torsional angles (−39°) and thus the syn interactions between OH and C-5 CH_3 groups in the conformations of 4*S*,5*R*,*M*.

Overall, these results illustrate that the dominating factor in relative stability and percent contribution is the presence of an intramolecular hydrogen bond between the hydrogen of the hemiaminal OH and the nitrogen atom of the pyridine ring bonded to N-3. The next factor is the preference of the anti orientation between C-5 methyl and OH group. The experimental percentages for Hemiaminal **7** isomers confirm that the same trend is observed for Hemiaminal **7**.

4 | CONCLUSION

In this study, 2-iminothiazolidin-4-one derivatives containing pyridine rings on their structures were easily reduced to their corresponding 3-(pyridin-2-yl)-2-(pyridin-2-ylimino) thiazolidin-4-ol derivatives diastereoselectively. The stereochemistry of the synthesized hemiaminals was clarified by 2D-NOESY experiments, and the ratio of the isomers was determined by ^{1}H NMR. The synthesized hemiaminals have been shown to be stable due to the formation of an intramolecular hydrogen bonding with a six-membered ring with N-3 pyridyl nitrogen and the hemiaminal OH group. In this way, the *RM* and *SP* enantiomeric pair of Hemiaminal **6** has been isolated. The racemic nature of the product has been shown by ^{1}H NMR in the presence of 1 equivalent of chiral auxiliary (*R*)-TFAE. Percent abundance of the diastereomers of Hemiaminals **6**, **7** and **8** was determined from the ^{1}H NMR spectra. Computational analysis of the percent contributions of all stereoisomers for Hemiaminals **6** and **8** are consistent with the experimental data and reveals the importance of the intramolecular hydrogen bond in the stabilities of such hemiaminals. In line with our previous study on 2-phenylimino-3-phenyl-4-hydroxythiazolidine,[4] we propose that the intramolecular hydrogen bond retards the dehydration of such hemiaminals and thus enhances their stabilities.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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