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Preparation and mechanistic studies of 2-substituted Bisthiazolidines by imine exchange.

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Abstract

Bisthiazolidines (BTZ) are bicyclic compounds considered penicillin analogs that inhibit the full range of Metallo- β -Lactamases (MBLs) and potentiate β -lactam activity against resistant bacteria. Herein we present a new methodology to prepare 2-substituted bisthiazolidines by aldehyde exchange. Thirteen new bisthiazolidines were prepared using this methodology, with yields ranged from 31 to 75%. The reaction is based on *in situ* imines formation, which are able to exchange side chains. The reaction intermediates were studied based on NMR experiments and a key imine **1b-II** could be detected in the reaction mixture. Furthermore, a DFT computational analysis was performed to gain insights into the reaction mechanism, allowing us to unveil the different pathways and their activation barriers within the synthetic route. The results suggest that the most favorable route involve the formation of the thiazolidine **1b-III** by i) a N-assisted N-C bond cleavage, and ii) a thiol-mediated 5 *endo*-trig cyclization followed by a C-N bond cleavage. In contrast with previously reported evidence, the imine metathesis was discarded as a plausible pathway. Finally, the reaction of **1b-III** with aldehyde **2a** leads to bicycle **4a** *via* the iminium ion **1b-V**.

Graphical Abstract

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Supporting information available: copies of ¹H and ¹³C spectra this material is available

Keywords

bisthiazolidines; imine exchange; metathesis microwave chemistry

Introduction

Bisthiazolidines[1] (**1**) are enantiomerically pure bicycles we have previously prepared in high yields (Figure 1).[2] Interestingly, they display activity against Metallo- β -Lactamases (MBLs), a diverse set of enzymes that catalyze the hydrolysis of a broad range of β -lactam drugs including carbapenems.[3,4] These compounds have been recently characterized as crossclass inhibitors against seven different MBLs, some of clinical relevance like NDM-1, VIM-2, and L1. [2,5–7]

Bicycles **1** are obtained in a tandem reaction by double condensation of L-aminothiols with two molecules of mercaptoacetaldehyde. Attempts to isolate the thiazolidine intermediate failed and the bicyclic 2-mercaptomethyl bisthiazolidines products were always obtained in high yields (Figure 1). Therefore, the possibility to introduce a different substituent in the position 2 of the heterocycle was limited, since it was not possible to isolate the thiazolidine intermediate that could react with a different aldehyde (R^3CHO).

Thiazolidines are imino-type compound, having the ability to exchange at the acetalic position with different aldehydes.[8–11] Imine exchange is a process triggered by acid catalysis,[12] amine[13,14] or transition metal complexes containing a metal-imido group $M=NR$ (M = Zr,[15] Mo,[16] Nb,[17] Ti,[18] Hf[19]). We envisioned the potentiality of this phenomenon in bisthiazolidines as well.

The present work explores the synthesis of 2-substituted bisthiazolidines with alkyl or aryl chains by exchanging 2-mercaptomethyl bisthiazolidines with different aldehydes. The mechanistic details of the synthetic route were unraveled using a combined NMR spectroscopic and *in silico*.

Results and Discussion

Bisthiazolidine **1a**, and isobutyraldehyde **2a** were selected as a model for the exchange reaction. We first assayed the reaction in MeOH, both in absence of catalyst or using additives as *p*-TsOH ac.,[20] NH₄OAc,[21] and L-Proline,[22] (see Table 1). The results showed that a catalyst is needed for the reaction to proceed, and the best conversion was obtained when using NH₄OAc.

Once the best catalyst was established, the use of microwave (MW) and conventional heating was explored to perform the exchange reaction. The results revealed that both heating methods gave similar yields but when using MW the reaction time was shorter (see entries 1 and 2 in Table 2). Consequently, we selected it as a source of heating to explore the optimal solvent for the exchange reaction.

Different organic solvents, including nonpolar, polar protic and aprotic, as well as aqueous buffer or neat conditions, were employed to study the effect over the reaction.[23] The results are compiled in Table 2. The reaction did not proceed in aqueous buffer at pH 5 or in MeCN (see entries 3 and 10, respectively), or in nonpolar solvents like DCM and DCE (see entries 5 and 4, respectively). The results evidenced that among the different solvents tried, MeOH and EtOH (entries 2 and 9, respectively) gave the best results in terms of reaction time and yield (55 and 60 %, respectively). Solvent free conditions led to lower yield (33 %), probably due to decomposition of starting material.

The ability of **1a** to exchange with aliphatic and aromatic aldehydes was studied using general conditions previously assayed, aldehyde (2eq), NH₄OAc (1.5 eq), MeOH, MW, 20' (Figure 2). The reaction was carried out with a diverse group of aldehydes, with yields ranging from 31% to 75%. Aliphatic aldehydes exchanged more efficiently than the aromatic ones, with yields ranging from 45% to 75%. Aromatic aldehydes were able to exchange only using MW heating, leading to the products in moderate yields (from 31 to 54%). Interestingly, conventional heating led to decomposition products, and the desired products could not be isolated. The electronic nature of the substituent in the aromatic ring did not present a clear influence in the exchange process; in this case, the best yield was obtained with *m*-tolualdehyde (54%).

Mercaptomethyl bisthiazolidines **1b** and **1c**, which bear different substituents at positions 7 and 8, were used to study the scope of the metathesis reaction (Figure 3). The compounds were submitted to the exchange conditions with aldehyde R¹CHO **2** (2 eq), and NH₄OAc (1.5 eq) in MW for 20'. Both heterocycles **1b-c** were able to exchange, leading to products **4a**, **4b** and **5** (65%, 21% and 52% yield respectively). The need of mercaptomethyl group for the exchange process was evaluated using 2-pentyl bisthiazolidine **4b**, with aldehyde **2a** (see Figure 3). The formation of the expected product **4a** was observed, indicating that 2-mercaptomethyl is not essential for the reaction.

Mechanistic studies

Bisthiazolidines are imino-type compounds, potentially able to reversible exchange a C=N linkage. Initially, the mechanism was thought to proceed through an imine exchange process

involving imines formed *in situ*. Basically, imine equilibration process is described to occur by three main types of reactions, hydrolysis, amine-imine exchange (transimination), or imine-imine exchange (imine metathesis).[24] We propose an exchange of species formed *in situ*.

To study the reaction, we performed time-course NMR experiments of the different reaction steps, aiming to identify key intermediate products. The reactions were performed in MeOD- d_4 and monitored using 1D ^1H and 2D ^1H , ^{13}C -HSQC and ^1H , ^{15}N -HMBC NMR spectra.

Isobutylimine formation, step A)

First, we studied the initial equilibration process of aldehyde **2a** (2 eq) with NH_4OAc (1.5 eq) in MeOD- d_4 in an NMR tube at room temperature. During this reaction we observed the formation of a complex mixture of species, and the progressive deuteration of the α -position of the starting aldehyde, the imine **III** and the intermediate product (carbinolamine **II**). Based on the NMR analyses we proposed the deuteration mechanism shown in Figure 4

When the aldehyde **2a** is dissolved in MeOD- d_4 , an equilibrium is established with the hemiacetal **I**. Upon addition of NH_4OAc , key proton resonances corresponding to the carbinolamine **II**, imine **III**, and enamine **IV** could be observed at 3.84, 7.64 and 6.39 ppm, respectively. The equilibrium between compounds **II** and **III** is confirmed by the observation of an exchange peak in the 1D ^1H , ^1H -NOESY spectra from the imine proton of compound **III** to the proton attached to the hemiaminal carbon in compound **II** (Figure 5).

The formation of the deuterated species started immediately after the addition of NH_4OAc , observed mainly as a change in the signal multiplicity from doublet to singlet due to the presence of a deuterium. A gradual increase of the ratio of the aldehyde protons of **2a-d** (9.59 ppm, s) and **2a** (9.59 ppm, d, $^3J_{\text{H,H}} = 1.1$ Hz) could be observed through time (Figure 6). The same process occurred for the imine protons of **III-d** (7.63 ppm, s) and **III** (7.64 ppm, d, $^3J_{\text{H,H}} = 5.6$ Hz), as well as the carbinolamine protons of **II-d** (3.82 ppm, s) and **II** (3.82 ppm, d, $^3J_{\text{H,H}} = 6.0$ Hz). The deuteration of the aforementioned species is almost complete after two hours of reaction. A gradual decrease in the intensity of the enamine proton resonance of compound **IV** (6.36 ppm, s) could also be observed, leading to a nearly complete disappearance of the signal after eight hours of reaction. An increase in the intensity of the hemiacetal proton resonance of the deuterated compound **I-d** (4.17 ppm, s) can also be observed in the ^1H NMR spectra (data not shown), with a concomitant drop of the respective signal of **I** (4.17 ppm, d, $^3J_{\text{H,H}} = 5.7$ Hz).

Imine intermediate formation, step B)

After a two-hour reaction of aldehyde **2a** with NH_4OAc in MeOD- d_4 , the imine proton resonance of deuterated **III-d** was observed as a singlet at 7.63 ppm (see Figure 7A). The ^{13}C and ^{15}N resonances of the imine moiety of compound **III-d** were observed at 172.7 ppm and -217.1 ppm, respectively. These chemical shifts were obtained from the corresponding ^1H , ^{13}C -HSQC and ^1H , ^{15}N -HMBC spectra, and the nitrogen chemical shift is informed using MeNO_2 as external reference.[25]

The resonance of the imine **III-d** disappeared immediately after the addition of bisthiazolidine **1b** (1 eq), and two new resonances (both broad singlets) can be observed at 7.58 and 7.55 ppm (Figure 7B), corresponding to two diastereomers of **1b-II**. In the $^1\text{H},^{13}\text{C}$ -HSQC spectrum these protons correlate to carbon resonances at 171.8 and 171.9 ppm, respectively, whereas the $^1\text{H},^{15}\text{N}$ -HMBC spectrum revealed two-bond correlations from the aforementioned protons to nitrogen resonances located at -215.2 ppm.

Product formation, step C)

After heating the reaction in the NMR tube at $50\text{ }^\circ\text{C}$ for 120 min, the aforementioned resonances at 7.58 and 7.55 ppm completely disappeared, and just a few minor signals were observed in the region between 7.62–7.44 ppm (Figure 7C). The resonances of the final product **4-d** could be identified in other regions of the spectrum.

Based on the above-mentioned ^1H -NMR analysis we proposed the mechanism depicted in Figure 8. The imine **III-d** is formed in the reaction media, as observed by NMR, step A). The iminium specie **1b-I** could be formed by bisthiazolidine **1b** opening, which was not observed in the ^1H -NMR spectrum. Imine Nitrogen of **III-d** would attack the iminium carbon of compound **1b-I** to produce a new imine intermediate **1b-II**, observed in the NMR spectra as a diastereomeric mixture, step B). The structure of **1b-II** was proposed, based on spectroscopic analysis on chemical shifts of ^1H (7.58 bs and 7.55 bs), ^{13}C (171.8 and 171.9), and ^{15}N (-215.2), see Figure 8B and Figures S2–5 in the supporting information. When the reaction was heated at $50\text{ }^\circ\text{C}$ for 2h, the exchange took place. Intermediate **1b-II** then led to the product **4a-d** as the main reaction product.

Theoretical calculations

To gain insights into the mechanism of step C, we conducted DFT calculations to the exchange process on the intermediate **1b-II**. All the stereochemical possibilities were taken into account (see Figure S7 and S8 for details). The summarized results are depicted in Figure 9.

The mechanistic proposal begins with the protonation of **1b-II** at the amine or imine N atoms, mediated by NH_4OAc catalyst. This triggers three different mechanistic pathways to form **4a**: i) thiazolidine **1b-III** formation by N-assisted N-C bond cleavage, ii) thiazolidine **1b-III** formation assisted by the thiol group of **1b-II** via a 5 *endo*-trig cyclization, followed by the C-N bond cleavage, and iii) imine metathesis via an azetidine intermediate, as proposed by Messmer *et al.* for aromatic imines,[26] giving rise to the formation of iminium ion **1b-V**.

The iminium ion **1b-V** is a common intermediate for all the routes, its intramolecular cyclization led to bisthiazolidine **4a**.

According to the computed activation barriers ($G^\ddagger$) at $50\text{ }^\circ\text{C}$ (Figure 9 B), the lowest-activation-energy process involves the formation of the thiazolidine **1b-III** by pathway i) (depicted in green in Figure 9 A), followed by the reaction with aldehyde **2a** to form the iminium ion **1b-V**. Finally its intramolecular cyclization leads to **4a** (shown in black in Figure 9 A). Considering all the stereochemical variants, the activation free energy

barriers for the lowest-activation-energy paths are 21.3 and 18.3 kcal/mol (TS₁ and TS₇, respectively; see Figure 9 B and S9). The 5 *endo*-trig cyclization followed by the C-N bond cleavage (pathway ii, shown in blue in Figure 9) also contribute to the formation of intermediate **1b-III** (24%), with a close activation barrier (22.1 kcal/mol, see TS₂ structure in Figure 9 B). Nevertheless, the imine metathesis (route iii, depicted in red in Figure 9 A) was ruled out, since it exhibits higher energy transition states (TS₄ and TS₅, shown in Figure 9 B and S9). Indeed, the free-energy difference between the global activation barriers of pathways i) and iii) is $\Delta G^\ddagger_{TS5-TS1} = 8.1$ kcal/mol.

Finally, the theoretical diastereomeric ratio predicted for **4a** under thermodynamic control is *syn/anti* (99.5:0.5), in accordance to the experimental value *syn/anti* (90:10). This validates the computational methods employed and gives evidence that the equilibrium was reached. The thermodynamic preference for the *syn* diastereomers can be accounted for by their structural features (Figure S10). The *syn* arrangement of the groups triggers a bending conformation of the molecules, separating the bulky groups and relieving the steric repulsion.

Conclusions

In summary, we have developed a new methodology to introduce alkyl and aryl substituents at position 2 of Bisthiazolidine ring with yields up to 75%. These findings could be useful to prepare new analogs of bisthiazolidines as MBLs inhibitors. The reaction occurs by the *in situ* formation of imines followed by exchange, using NH₄OAc as promoter. The catalyst plays a dual role by forming the necessary imine for the exchange and giving the acidic media to promote it. A key imine intermediate (**1b-II**) was identified by NMR spectroscopy and chemical shifts of the different ¹⁵N-imine were reported. DFT calculations allowed as to furnish a clear picture of the mechanism and activation barriers for the transformation of imine **1b-II** into **4a**. The most favorable routes involve the formation of thiazolidine **1b-III** by i) N-assisted N-C bond cleavage, and ii) a thiol-mediated 5 *endo*-trig cyclization followed by a C-N bond cleavage. Thiazolidine **1b-III** then reacts with aldehyde **2a** to give **4a**. Altogether these results contribute to a better understanding of the exchange process, adding new information to the scarce data available.

Experimental Section

1. General Methods

Reactions were monitored by analytical thin layer chromatography (TLC) on 0.25 mm silica gel coated plastic sheets (SIL G/UV 254). Flash chromatography on Silica gel 60 (40 μm average particle diameter) was used to purify the crude reaction mixtures. All NMR spectra were recorded in CDCl₃-*d* at 300 K on a Bruker Avance 400 MHz spectrometer equipped with a 5 mm QXI probe and on Avance III 400 MHz spectrometer equipped with a 5 mm BBOF plus probe. Chemical shifts (δ) are expressed in ppm using tetramethylsilane (TMS) as internal reference, and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). The assignments of ¹H and ¹³C NMR resonances were made based on a combination of ¹H, ¹H-COSY, ¹H, ¹³C-HSQC, and ¹H, ¹³C-HMBC spectra. The ¹⁵N chemical shifts were determined using ¹H, ¹⁵N-HMBC experiments, and referenced

to MeNO₂. Microwave reactions were performed using a single-mode from CEM Discover. All microwave reactions were performed in a sealed tube reaction condition. Reaction temperatures were monitored by an internal probe, and the temperature was maintained in each experiment. All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Yields are reported for chromatographic and spectroscopic (¹H and ¹³C NMR) pure compounds unless otherwise stated. HRMS spectra were recorded on Xevo G2S Q-TOF (Waters Corp) and MicroTOF-QTM (Bruker Daltonics) mass spectrometers. ESI(+)-LCMS spectra were recorded on LTQ XL Thermo. Optical rotation was measured using a Kruss Optronic GmbH P8000 polarimeter with a 0.5 mL cell (concentration c given as g/100mL).

2. Synthetic procedures

(2R, 5S, 8R)-8-Carboxyl-2-mercaptomethyl-1-aza-3,6-dithiobicyclo[3.3.0]octane

(syn 1a).—To a stirred solution of L-cysteine (1 g, 8.3 mmol) in buffer acetate pH 5 (100 mL), was added 1,4-dithiane-2,5-dithiol (1.5 g, 9.9 mmol). The mixture was heated at reflux for 2 h. Then, it was cooled and poured into a saturated aqueous solution of NaCl (30 mL), extracted with AcOEt (5×30 mL), dried (Na₂SO₄) and filtered. The solvent was removed under reduced pressure and the residue was purified by chromatography on SiO₂ (nHex/EtOAc/AcOH 7:3:0.1) to give compound **1a** (1.3 g, 65 %, *syn/anti* 92:08) as a solid: ¹H NMR δ 5.05 (dd, *J* = 5.8, 4.2 Hz, 1H), 4.32 (t, *J* = 6.9 Hz, 1H), 4.25 (dd, *J* = 7.1, 3.3 Hz, 1H), 3.55 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.43 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.33 (dd, *J* = 11.4, 7.1 Hz, 1H), 3.11 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.81 (dd, *J* = 8.5, 6.9 Hz, 2H), 1.86 (t, *J* = 8.5 Hz, 1H_{sh}). The spectroscopic properties were identical as described in literature.⁵

(2RS, 5SR)-2-Mercaptomethyl-1-aza-3,6-dithiobicyclo[3.3.0]octane (± syn 1b)—

Prepared in analogous route as described for **1a**, starting from cysteamine.HCl, to give **1b** (2.6 g, 74 %, *syn/anti* 92:08) as an oil: ¹H NMR δ 4.97 (dd, *J* = 5.2, 3.7 Hz, 1H), 4.24 (dd, *J* = 7.0, 6.0 Hz, 1H), 3.54 (ddd, *J* = 11.6, 5.2, 0.5 Hz, 1H), 3.48 (ddd, *J* = 11.5, 5.7, 4.8 Hz, 1H), 3.21 (ddd, *J* = 11.5, 7.2, 6.6 Hz, 1H), 3.12 (m, 1H), 3.08 (m, 2H), 2.82 (ddd, 13.6, 7.6, 7.0 Hz, 1H), 2.65 (ddd, *J* = 13.6, 9.1, 6.0 Hz, 1H), 1.84 (dd, *J* = 9.1, 7.6 Hz, 1H); ¹³C NMR δ 74.5, 73.2, 57.1, 38.4, 33.5, 31.8. The spectroscopic properties were identical as described in literature.¹

(2R, 5S, 8R)-8-Carboxyl-7-dimethyl-2-mercaptomethyl-1-aza-3,6-

dithiobicyclo[3.3.0]octane (syn 1c).—Prepared in analogous route as described for **1a**, starting from L-penicillamine to give **1c** as a white solid: ¹H NMR 4.98 (dd, *J* = 6.6, 5.4 Hz, 1H), 3.80 (s, 1H), 4.31 (t, *J* = 7.3 Hz, 1H), 3.43 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.06 (dd, *J* = 11.7, 5.4 Hz, 1H), 1.89 (t, *J* = 8.7 Hz, 1H_{sh}), 2.81 (m, 2H), 1.62 (s, 3H), 1.52 (s, 3H). The spectroscopic properties were identical as described in literature.⁵

(2R, 5S, 8R)-8-Carboxyl-2-Isopropyl-1-aza-3,6-dithiobicyclo[3.3.0]octane (3a)—

To a solution of bisthiazolidine **1a** (100 mg, 0.42 mmol) in dry MeOH (1 mL) was added isobutyraldehyde **2a** (0.077 mL, 0.84 mmol) and NH₄OAc (48.5 mg, 0.63 mmol). The reaction mixture was stirred at 65°C for 20' under microwave irradiation (50 W). The solvent was evaporated under reduced pressure and the residue was purified by column

chromatography on flash silica gel (*n*Hex/EtOAc 7:3 + 0.1% AcOH) to give **3a** (64 mg, 55%) as a colorless oil: ^1H NMR δ 5.02 (m, 1H), 4.12 (dd, J = 7.1, 3.0 Hz, 1H), 4.06 (d, J = 6.6 Hz, 1H), 3.46 (dd, J = 11.9, 5.7 Hz, 1H), 3.42 (dd, J = 11.4, 3.0 Hz, 1H), 3.33 (dd, J = 11.3, 7.1 Hz, 1H), 3.02 (dd, J = 11.9, 4.3 Hz, 1H), 1.91 (dq, J = 13.3, 6.7 Hz, 1H), 1.04 (d, J = 6.6 Hz, 1H); ^{13}C NMR δ 173.6, 79.7, 73.9, 71.2, 38.2, 35.3, 33.3, 20.0, 18.5; $[\alpha]_{\text{D}}^{21}$ -31.3° (c 3.2, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_9\text{H}_{16}\text{NO}_2\text{S}_2$ 234.0617; Found 234.0607.

(2R, 5S, 8R)-8-Carboxyl-2-ethyl-1-aza-3,6-dithiobicyclo[3.3.0]octane (3b)—

Prepared in an analogous route as described for **3a** starting from **1a** and propionaldehyde **2b** to give **3b** (69 mg, 75%) as an oil: ^1H NMR δ 5.04 (1H, t, J = 5.6), 4.18 (dd, J = 5.4, 8.3 Hz, 1H), 4.09 (dd, J = 3.6, 7.1 Hz, 1H), 3.45 (m, 1H), 3.37 (m, 2H), 3.05 (dd, J = 5.1, 8.3 Hz, 1H), 1.91 (m, 1H), 1.71 (tt, J = 7.3, 14.3 Hz, 1H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 172.6, 74.6, 73.2, 70.2, 37.9, 33.3, 31.6, 11.3; $[\alpha]_{\text{D}}^{21}$ $+96.1$ (c 0.20, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_8\text{H}_{14}\text{NO}_2\text{S}_2$ 220.0466; Found 220.0432.

(2R, 5S, 8R)-8-Carboxyl-2-((RS)-2,6-dimethylhept-5-en-1-yl)-1-aza-3,6-dithiobicyclo[3.3.0]octane (3c)—

Prepared in an analogous route as described for **3a**, starting from **1a** and $\pm$ citronellal **2c** to give **3c** diastereomeric mixture (142 mg, 54%, *syn* 2RS/*anti* 2RS 90:10) as an oil: (2RS) *syn*-**3c**: ^1H NMR δ 5.07 (m, 2H), 4.32 (m, 1H), 4.10 (m, 1H), 3.46 (m, 1H), 3.37 (m, 2H), 3.05 (m, 1H), 1.97 (m, 2H), 1.75 (m, 1H), 1.69 (s, 3H), 1.65 (m, 1H), 1.61 (s, 3H), 1.54 (m, 1H), 1.37 (m, 1H), 1.15 (m), 0.92 (q, J = 6.4 Hz, 3H); (2RorS) *syn*-**3c** ^{13}C NMR δ 174.1, 131.3, 124.3, 73.1, 71.1, 69.2, 46.1, 38.0, 37.4, 33.5, 30.6, 25.6, 25.2, 19.8, 17.6; (2RorS) *syn* **3c** ^{13}C NMR δ 174.1, 131.3, 124.2, 72.9, 71.1, 69.11, 45.4, 37.6, 36.1, 33.5, 30.4, 25.6, 25.1, 19.7, 17.5; (2RS) *anti* **3c** ^1H NMR δ 4.87 (m, 1H), 4.70 (m, 1H); (2RorS) *anti* **3c** ^{13}C NMR δ 70.9, 19.1; ^{13}C NMR δ 70.8, 19.0; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_2\text{S}_2\text{Na}$ 352.1375; Found 352.1394

(8R)-Carboxyl-1-aza-3,6-dithiobicyclo[3.3.0]octane (3d)—Prepared in an analogous route as described for **3a** starting from **1a** and formaldehyde **2d** to give **3d** (39 mg, 45%) as a yellow oil: ^1H NMR δ 4.93 (dd, J = 6.4, 4.4 Hz, 1H), 4.30 (d, J = 10.2 Hz, 1H), 4.12 (d, J = 10.2 Hz, 1H), 4.10 (m, 1H), 3.41 (m, 3H), 3.06 (dd, J = 11.8, 4.3 Hz, 1H); ^{13}C NMR δ 173.3, 72.8, 70.0, 58.2, 40.0, 34.2; $[\alpha]_{\text{D}}^{21}$ $+83.6$ (c 0.43, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_6\text{H}_{10}\text{NO}_2\text{S}_2$ 192.0147; Found 192.0141.

(2R, 5S, 8R)-8-Carboxyl-2-(*m*-tolyl)-1-aza-3,6-dithiobicyclo[3.3.0]octane (3e)—

Prepared in an analogous route as described for **3a** starting from **1a** and 3-methylbenzaldehyde **2e** to give **3e** (64 mg, 54%) as colorless oil: ^1H NMR δ 7.31 (m, 2H), 7.28 (m, 1H), 7.16 (m, 1H), 5.28 (dd, J = 6.3, 4.2 Hz, 1H), 5.16 (s, 1H), 4.10 (dd, J = 7.4, 2.8 Hz, 1H), 3.60 (dd, J = 11.7, 6.3 Hz, 1H), 3.52 (dd, J = 11.5, 2.7 Hz), 3.40 (dd, J = 11.5, 7.4 Hz, 2H), 3.24 (dd, J = 11.8, 4.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR δ 173.8, 138.8, 138.3, 130.0, 129.0, 128.6, 125.1, 74.18, 72.9, 68.1, 36.9, 33.5, 21.6; $[\alpha]_{\text{D}}^{21}$ $+196.0^\circ$ (c 3.2, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}_2\text{Na}$ 304.0436; Found 304.0433

(2R, 5S, 8R)-8-Carboxyl-2-phenyl-1-aza-3,6-dithiobicyclo[3.3.0]octane (3f)—

Prepared in an analogous route as described for **3a** starting from **1a** and benzaldehyde **2f** to give **3f** (56 mg, 50%) as an oil: ^1H NMR δ 7.52 (m, 2H), 7.35 (m, 3H), 5.30 (dd, J = 6.3, 4.1 Hz, 1H), 5.21 (s, 1H), 4.12 (dd, J = 7.4, 2.8 Hz, 1H), 3.60 (dd, J = 11.8, 6.3 Hz, 1H), 3.45 (m, 1H), 3.24 (dd, J = 11.8, 4.1 Hz, 1H); ^{13}C NMR δ 173.2, 138.3, 129.0, 128.9, 127.8, 74.0, 72.9, 68.0, 36.9, 33.4; $[\alpha]_{\text{D}}^{21} +199.7^\circ$ (c 2.6, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}_2$ 268.0466; Found 268.0462

(2R, 5S, 8R)-8-Carboxyl-2-(4-methoxyphenyl)-1-aza-3,6-

dithiobicyclo[3.3.0]octane (3g)—Prepared in an analogous route as described for **3a** starting from **1a** and 4-methoxybenzaldehyde **2g** to give **3g** (42 mg, 40%) as yellow oil: ^1H NMR δ 7.46 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.28 (dd, J = 6.4, 4.1 Hz, 1H), 5.17 (s, 1H), 4.10 (dd, J = 7.4, 2.7 Hz, 1H), 3.84 (s, 3H), 3.62 (dd, J = 11.8, 6.4 Hz, 1H), 3.54 (dd, J = 11.5, 2.7 Hz, 1H), 3.41 (dd, J = 11.5, 7.5 Hz, 1H), 3.26 (dd, J = 11.8, 4.1 Hz, 1H); ^{13}C NMR δ 171.7, 160.3, 132.0, 129.3, 114.5, 73.6, 72.5, 67.8, 55.4, 36.5, 33.1; $[\alpha]_{\text{D}}^{21} +127.4^\circ$ (c 2.1, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_3\text{S}_2$ 298.0572; Found 297.0554

(2R, 5S, 8R)-8-Carboxyl-2-(3-bromophenyl)-1-aza-3,6-dithiobicyclo[3.3.0]octane (3h)—

Prepared in an analogous route as described for **3a** starting from **1a** and 3-bromobenzaldehyde **2h** to give **3h** (62 mg, 42%) as colorless oil: ^1H NMR δ 7.68 (m, 1H), 7.46 (m, 2H), 7.24 (m, 1H), 5.27 (dd, J = 6.1, 3.3 Hz, 1H), 5.18 (s, 1H), 4.14 (dd, J = 6.8, 3.9 Hz, 1H), 3.59 (dd, J = 11.7, 6.2 Hz, 1H), 3.51 (dd, 11.4, 3.3 Hz, 1H), 3.42 (m, 2H), 3.23 (dd, J = 11.7, 3.4 Hz, 1H); ^{13}C NMR δ 174.0, 141.5, 131.9, 130.8, 130.4, 126.4, 122.8, 74.0, 72.4, 68.2, 37.2, 33.7; $[\alpha]_{\text{D}}^{21} +115.0^\circ$ (c 3.0, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{13}\text{BrNO}_2\text{S}_2$ 345.9571; Found 345.9563

(2R, 5S, 8R)-8-Carboxyl-2-(4-(trifluoromethyl)-1-aza-3,6-

dithiobicyclo[3.3.0]octane (3i)—Prepared in an analogous route as described for **3a** starting from **1a** and 4-(trifluoromethyl)benzaldehyde **2i** to give **3i** (44 mg, 31%) as colorless oil: ^1H NMR δ 7.65 (q, J = 8.6 Hz, 4H), 5.29 (m, 2H), 4.13 (dd, J = 7.0, 3.9 Hz, 1H), 3.58 (dd, J = 11.8, 6.1 Hz, 1H), 3.46 (m, 2H), 3.25 (dd, J = 11.8, 3.2 Hz, 1H); ^{13}C NMR δ 174.5, 143.6, 130.3 (q, J_{CF} = 32.4 Hz), 128.0, 125.7 (q, J_{CF} = 3.7 Hz), 123.9 (q, J_{CF} = 272.2 Hz), 74.0, 72.5, 68.3, 37.5, 33.9; $[\alpha]_{\text{D}}^{21} +265.0^\circ$ (c 2.2, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{NO}_2\text{S}_2$ 336.0340; Found 336.0351

(2R, 5S, 8R)-8-Carboxyl-2-(4-chlorophenyl)-1-aza-3,6-dithiobicyclo[3.3.0]octane (3j)—

Prepared in an analogous route as described for **3a** starting from **1a** and 4-chlorobenzaldehyde **2j** to give **3j** (43 mg, 34%) as colorless oil: ^1H NMR δ 7.47 (m, 2H), 7.33 (m, 2H), 5.29 (dd, J = 6.2, 3.4 Hz, 1H), 5.19 (s, 1H), 4.11 (dd, J = 6.7, 4.0 Hz, 1H), 3.58 (dd, J = 11.7, 6.2 Hz, 1H), 3.43 (m, 2H), 3.23 (dd, J = 11.7, 3.4 Hz, 1H); ^{13}C NMR δ 174.3, 137.6, 134.8, 129.3, 129.1, 74.1, 72.4, 68.1, 37.1, 33.8; $[\alpha]_{\text{D}}^{21} +173.0^\circ$ (c 2.1, MeOH); HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{12}\text{ClNO}_2\text{S}_2$ 302.0076; Found 302.0071

(2RS,5SR)-2-isopropyl-1-aza-3,6-dithiobicyclo[3.3.0]octane ($\pm$ syn **4a)**—Prepared in an analogous route as described for **3a** starting from **1b** and isobutyraldehyde **2a**, microwave irradiation was 40 min, to give **4a** as inseparable diastereomeric mixture (61 mg, 65%, *syn/anti* 90:10) as colorless oil: *syn-4a*: ^1H NMR δ 5.00 (dd, $J = 4.9, 3.1$ Hz, 1H), 3.91 (d, $J = 6.0$ Hz, 1H), 3.14 (m, 2H), 3.02 (m, 2H), 1.82 (m, 1H), 0.99 (dd, $J = 6.6, 4.9$ Hz, 6H); ^{13}C NMR δ 77.2, 75.8, 57.2, 37.7, 35.5, 31.8, 20.1, 17.8; *anti-4a*: ^1H NMR 4.56 (dd, $J = 8.4, 7.3$ Hz, 1H), 4.46 (d, $J = 10.3$ Hz, 1H), 3.46 (m, 1H), 3.25 (m, 2H), 1.94 (m, 1H), 1.16 (d, $J = 6.5$ Hz, 3H), 1.05 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR δ 79.5, 72.0, 45.6, 40.3, 32.7, 31.6, 22.3, 21.0; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_8\text{H}_{16}\text{NS}_2$ 190.0719; Found 190.0718.

(2RS, 5SR)-2-(2-deuteropropan-2-yl)-1-aza-3,6-dithiobicyclo[3.3.0]octane ($\pm$ **4a-d)**—To a solution of $\pm$ (2RS,5SR)-2-Mercaptomethyl-1-aza-3,6-dithiobicyclo[3.3.0]octane **1b** (20 mg, 0.10 mmol) in $\text{MeOD}-d_4$ (0.6 mL) was added isobutyraldehyde **2a** (0.018 mL, 0.21 mmol) and NH_4OAc (12 mg, 0.15 mmol). The reaction mixture was stirred at 65°C for 10' under microwave irradiation (50 W). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on flash silica gel (nHex/EtOAc 9:1) to give **4a-d** as a diastereomeric mixture (6 mg, 31 %, *syn/anti* 90:10) as yellow oil. *syn-4a-d*: ^1H -NMR δ 5.01 (dd, $J = 4.7, 3.2$ Hz, 1H), 3.91 (s, 1H), 3.45 (m, 2H), 3.15 (m, 2H), 3.06 (dd, $J = 11.5, 3.0$ Hz, 1H), 3.01 (m, 1H); ^{13}C NMR δ 77.2, 75.8, 57.1, 37.7, 35.0 (t, $J_{\text{C-D}} = 19.5$ Hz), 31.8, 20.0, 17.7; HRMS (ESI/Q-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_8\text{H}_{15}\text{DNS}_2$ 191.0781; Found 191.0784

(2RS,5SR)-2-pentyl-1-aza-3,6-dithiobicyclo[3.3.0]octane ($\pm$ syn/anti **4b)**—Prepared in an analogous route as described for **3a** starting from **1b** and hexanal, microwave irradiation was 60 min, to give **4b** as a diastereomeric mixture (79 mg, 21%, *syn/anti* 83:17) as a yellow oil: ^1H NMR δ 5.02 (dd, $J = 5.5, 3.3$ Hz, 1H), 4.73* (dd, $J = 8.4, 5.8$ Hz, 1H), 4.53* (m, 1H), 4.09 (dd, $J = 8.3, 5.0$ Hz, 1H), 3.50 (dd, $J = 11.4, 5.6$ Hz, 1H), 3.41 (m, 1H), 3.17* (m, 4H), 3.02 (m, 1H), 2.82* (m, 1H), 1.99* (m, 1H), 1.79 (m, 1H), 1.59 (m, 1H), 1.33 (m, 8H), 0.89 (t, $J = 6.9$ Hz, 4H), ^{13}C -NMR δ 75.2, 72.0*, 71.7*, 70.3, 55.5, 46.3*, 40.4*, 38.8, 36.7, 33.7*, 31.7*, 31.6, 28.00*, 26.9, 22.4, 14.0, 13.4* (*minor diastereomer); ESI(+)-LCMS m/z : 218.10 $[\text{M} + \text{H}]^+$

NMR

(2R, 5S, 8R)-8-Carboxyl-2-isopropyl-7,7-dimethyl-1-aza-3,6-dithiobicyclo[3.3.0]octane (5**)**—Prepared in an analogous route as described for **3a** starting from **1c** and isobutyraldehyde **2a**. The reaction mixture was stirred at 65°C for 60 min under microwave irradiation (50 W). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on flash silica gel to give **5** (50 mg, 52%) as an oil: ^1H -NMR δ 4.87 (t, $J = 6.5$ Hz, 1H), 4.03 (d, $J = 8.4$ Hz, 1H), 3.74 (s, 1H), 3.32 (dd, $J = 11.3, 6.7$ Hz, 1H), 3.00 (dd, $J = 11.3, 6.4$ Hz, 1H), 1.81 (m, 1H), 1.61 (s, 3H), 1.50 (s, 3H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR δ 174.0, 80.7, 77.6, 69.1, 55.1, 40.5, 35.9, 28.9, 28.1, 20.3, 19.6; $[\alpha]_{\text{D}}^{21} +173.0^\circ$ (c 2.1, MeOH) HRMS (ESI/Q-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_2\text{S}_2$ 262.0930; Found 262.0933.

3. Sample preparation for Mechanistic studies

Step A)—A solution of isobutylaldehyde (15 mg, 0.20 mmol), NH_4OAc (12 mg, 0.15 mmol) in CD_3OD (0.6 ml) was prepared in an NMR tube. The reaction was monitored by ^1H , ^1H - ^1H COSY, ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC-NMR, for 2 h at room temperature and the imine **III-d** was identified: ^1H NMR δ 7.63 (s), 0.81 (s); ^{13}C NMR δ 172.7, 33.5, 16.2.

Step B)—The bisthiazolidine **1b** (20 mg, 0.10 mmol) was added to the NMR tube of step A). The reaction was monitored at room temperature by ^1H , ^{13}C , ^1H - ^1H COSY, ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC-NMR, the Intermediate **1b-II** (dr 60:40) was identified: ^1H -NMR δ 7.58 (s), 7.56* (s) 4.32 (dd, $J = 7.6, 5.7$ Hz), 4.27* (m), 4.19 (bs), 4.14* (bs), 3.36 (m), 3.16* (m), 3.12 (m), 3.03* (m), 2.75 (m), 2.50 (m), 2.67 (m), 2.47 (m); ^{13}C NMR δ 171.9, 171.8*, 80.5*, 80.3, 71.1, 70.4*, 56.4*, 56.3, 38.8, 38.3, 33.5 (t, $J = 19.4$ Hz), 30.9, 30.8*, 18.4 (*minor diastereomer)

Step C)—The NMR tube of step B) was warming to 50°C for 2 h. The reaction was monitored by ^1H , ^1H - ^1H COSY, ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC-NMR.

4. Sample preparation for ^{15}N experiments

To perform the ^{15}N -HMBC experiments the procedure above described was followed using $^{15}\text{NH}_4\text{OAc}$ in step A).

5. Computational calculations

Initial geometries of all the stereoisomers were pre-optimized by molecular mechanics (MMFF94X forcefield; energy gradient = $0.01 \text{ kcal/mol/\AA}^3$), as implemented in MOE.[27] The solvent (methanol) was modeled by means of the Generalized Born model ($\epsilon = 33.1$). In order to explore the potential energy surface, a conformational search was performed using the LowModeMD search method,[28] with the same forcefield and solvation method, without cut-offs, and with a RMS gradient = $0.005 \text{ kcal/mol/\AA}^3$ (rejection limit = 100; RMSD limit = $0.25 \text{ \AA}$; energy window = 7 kcal/mol ; iteration limit = 10000).

The most stable conformations were selected and fully optimized by means of the density functional theory method (DFT),[29] employing the M06-2x functional,[30] which has been reported to have excellent across-the-board average performance in general thermochemistry and kinetics. [30] To represent the electronic wave function, the 6-31+G(d,p) basis set[31] was used, since 6-31+G(d) has showed satisfactory performance for similar systems.[32] The extra p polarization functions were added to hydrogen atoms to enhance the computational description of the hydrogen-mediated interactions.[33] The calculations were carried out without symmetry constraints and with an ultrafine integration grid, employing the Gaussian 09 code.[34] The influence of the solvent (methanol) was simulated by an IEFPCM method (implicit solvation), with radii and non-electrostatic terms from Truhlar and coworkers' SMD solvation model.[35] To verify the nature of each stationary state, the Hessian matrix was analytically calculated. The optimized geometries of the intermediates were found to have only real vibrational frequencies, whereas the transition states exhibited a single negative eigenvalue. This negative normal mode was

animated and examined in each case, confirming that it reflects the structural change in going from reactants to products. The computational results were rendered with Gaussview 5.0.[36]

Zero-point energies and thermal corrections were taken from unscaled analytical vibrational frequencies. The yield under kinetic control was estimated by means of the Transition State Theory,[37] using the Curtin-Hammett principle.[38]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Synthesis of mercaptomethyl bisthiazolidines **1**.

Figure 2.
Preparation of 2-substituted bisthiazolidines

Figure 3.

Compounds **1b**, **1c**, **1d**, and **4b** were used for the exchange in standard conditions R^1CHO (2 eq), NH_4OAc (1.5 eq), MeOH, MW, 65 °C, 50 W, and 20'.

Figure 4.

Proposed deuteration mechanism of aldehyde **2a** and imine **III** at the α -position of the carbonyl and imine functions, respectively, in $\text{MeOD-}d_4$.

Figure 5.

1D ^1H , ^1H -NOESY spectrum ($\tau_m = 500$ ms) recorded by selective irradiation of the imine protons of compounds **III** and **III-d**, 20' after the addition of NH_4OAc to the aldehyde **2a** in $\text{MeOD-}d_4$. An exchange peak can be observed from the imine proton of compounds **III** and **III-d** to the protons attached to the hemiaminal carbon of compounds **II** and **II-d**.

Figure 6.

Selected regions of the time-course ^1H NMR spectra of the reaction of aldehyde **2a** with NH_4OAc in $\text{MeOD}-d_4$, showing selected resonances of compounds **2a** (aldehyde proton), **II** (hemiaminal proton), **III** (imine proton), and **IV** (enamine proton), and their respective deuterated counterparts **2a-d**, **II-d** and **III-d**.

Figure 7:

^1H -NMR spectra of the reaction mixtures: A) **2a** (0.21 mmol), NH_4OAc (0.15 mmol) in $\text{MeOH-}d_4$ (0.6 mL), rt, 2 h, step 1; B) **2a** (0.21 mmol), NH_4OAc (0.15 mmol), Bisthiazolidine **1b** (0.10 mmol), $\text{MeOH-}d_4$ (0.6 mL), rt, $t = 02'$, step 2; C) idem B) after 2h at 50 °C. The ^{13}C and ^{15}N chemical shift of the atoms highlighted in red color were obtained from ^1H , ^{13}C -HSQC and ^1H , ^{15}N -HMBC correlations to the respective imine protons.

Figure 8.
Proposed exchange process mechanism.

Figure 9.

A) Mechanistic proposal. The activation barriers ($G^\ddagger$ at 50 °C) with respect to the reactant are included in kcal/mol for the lowest-activation-energy paths among the stereochemical variants. The distribution % under kinetic control (Curtin-Hammett principle) are also included for the different pathways. Diastereomer distribution for compound **4a** *syn/anti* (99.5:0.5) was determined at equilibrium. **B)** Predicted reaction profiles. The lowest-activation-energy process involves the green and black pathways (through TS1 and TS7). The DFT calculations were carried out at M062×/6–31+G(d,p) level of theory.

Table 1.

Results of the exchange reactions using different catalysts.

Entry	Catalyst	3a conversion (%) ^[a]
1	-	0
2	p-TsOH (0.1 eq)	0
3	NH ₄ OAc (1.5 eq)	60
4	L-Pro (1.5 eq)	14

^[a]The conversion was determined using ¹H-NMR spectroscopy

Table 2.

Solvent reaction screening for the conversion.

Entry	Conditions, solvent, T, time	3a conversion (%) ^[a]	3a yield (%) ^[b]
1	MeOH, reflux, 3 h	60	60
2	MeOH, MW 65 °C, 20'	60	55
3	BA ^[c] pH 5, reflux, 3 h	0	nd ^[d]
4	DCE, MW 65 °C, 20'	0	nd ^[d]
5	DCM, MW 65 °C, 20'	0	nd ^[d]
6	<i>i</i> PrOH, MW 65 °C, 20'	28	20
7	TFE, MW 65 °C, 20'	45	45
8	BuOH, MW 65 °C, 20'	11	nd ^[d]
9	EtOH, MW 65 °C, 20'	65	60
10	MeCN, MW 65 °C, 20'	0	nd ^[d]
11	DMF, MW 65 °C, 20'	34	23
12	Neat, MW 65 °C, 5'	100	33
10	MeCN, MW 65 °C, 20'	0	nd ^[d]

^aThe conversion was determined using ¹H-NMR spectroscopy.^bIsolated yield obtained after chromatographic purification. nd = not determined. BA = buffer acetate pH 5.