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Thorpe–Ingold effect in the reaction of vicinal amino primary alcohol hydrogen sulfates and carbon disulfide

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ABSTRACT

The Thorpe–Ingold effect is a key factor that affects the ring-closure rates and efficiency, as well as the structure of products in some ring-closure reactions. The reaction of vicinal amino primary alcohol hydrogen sulfates and carbon disulfide in the presence of potassium hydroxide produces the desired 4,4-disubstituted thiazolidine-2-thiones, and their isomers 5,5-disubstituted derivatives companying with their oxygen analogues 4,4-disubstituted oxazolidine-2-thiones. The formation of 5,5-disubstituted thiazolidine-2-thiones was rationalized via 2,2-disubstituted aziridine-1-carbodithioate intermediates, which were generated due to the Thorpe–Ingold effect. 4,4-Disubstituted oxazolidine-2-thiones were generated from carbon disulfide and free amino alcohols yielded via basic hydrolysis of active amino alcohol hydrogen sulfates in the reaction system.

1. Introduction

The Thorpe–Ingold effect,[1] also named the *gem*-dialkyl effect, is an important parameter that remarkably affects the ring-closure rates and efficiency.[2] In 2005, Jung and Piizzi concluded that only a few literatures reported the application of the Thorpe–Ingold effect in the formation of small rings due to the strong ring tension.[3] Even though, the recent reports on the geminal dialkyl effect were still focusing on the medium ring (five- to seven-membered ring) systems.[4] Bachrach,[5] Kostal, and Jorgensen[6] reported the *gem*-dimethyl effect in the four- and three-membered ring systems, however, both of them used the computational method, which is lack of the experimental observation.

Thiazolidine-2-thiones are a class of important organic intermediates, especially in the application of pharmaceutical chemistry and asymmetric synthesis. For example, *N*-acyl 4-substituted thiazolidine-2-thiones have been widely applied as chiral auxiliaries in numerous asymmetric transformations.[7] As their homologs, *gem*-disubstituted thiazolidine-2-thiones were also reported in these fields.[8] Several 4,4-disubstituted thiazolidine-2-thiones have been prepared from 2,2-disubstituted 2-amino ethanol hydrogen sulfates and carbon disulfide.[9] Herein, we found that both 4,4- and 5,5-disubstituted thiazolidine-2-thiones were obtained from the reaction of vicinal amino primary alcohol hydrogen sulfates and carbon disulfide via the generation of *gem*-disubstituted aziridine derivatives due to the Thorpe–Ingold effect.

2. Results and discussion

2.1. Reaction of vicinal amino primary alcohol hydrogen sulfates and carbon disulfide

We have reported that amino alcohol hydrogen sulfates, prepared from vicinal amino alcohols and sulfuric acid, reacted with carbon disulfide under basic conditions to afford corresponding substituted thiazolidine-2-thiones in moderate to good yields.[10] However, in the synthesis of 4,4-disubstituted thiazolidine-2-thiones, the reaction products were very complicated, so we tried to investigate these reactions systematically and in detailed herein.

We initially esterified 2-amino-2-methylpropanol (**5a**) with sulfuric acid to form its corresponding hydrogen sulfate (**1a**), which was subjected the ring-closure with carbon disulfide under basic conditions (Table 1, entry 1). During the ring-closure process, TLC showed that there were two excrescent products **3a** (yield 31%, R_f=0.25, PE/EA [petroleum ether (60–90 °C)/ethyl acetate]=3:1, v/v) and **4a** (yield 13%, R_f=0.33, PE/EA=3:1, v/v) besides the desired product 4,4-dimethylthiazolidine-2-thione (**2a**, yield 41%, R_f=0.44, PE/EA=3:1, v/v). 4,4-Dimethyloxazolidine-2-thione (**3a**) was identified by comparing with the literature reported spectral data.[11] HRMS data indicated that **4a** was the structural isomer of **2a**, and an absorption peak at 201.5 ppm in ^{13}C NMR demonstrated the

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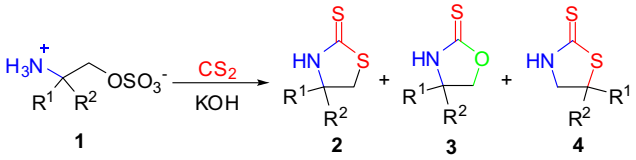
existence of the thiocarbonyl group (S=C–S). All of these information suggested that **4a** was 5,5-dimethyl-thiazolidine-2-thiones (Scheme 1). As we know, during the sulfuric acid esterification process, high temperature and vigorous stirring were needed to make the reaction complete, however, it was really difficult for the magnetic stir bar to stir the viscous reaction system. Due to the observation of the formation of 4,4-dimethyloxazolidine-2-thione (**3a**), we first assumed that the esterification was incomplete, and the residual free amino alcohol underwent the ring-closure with carbon disulfide directly.

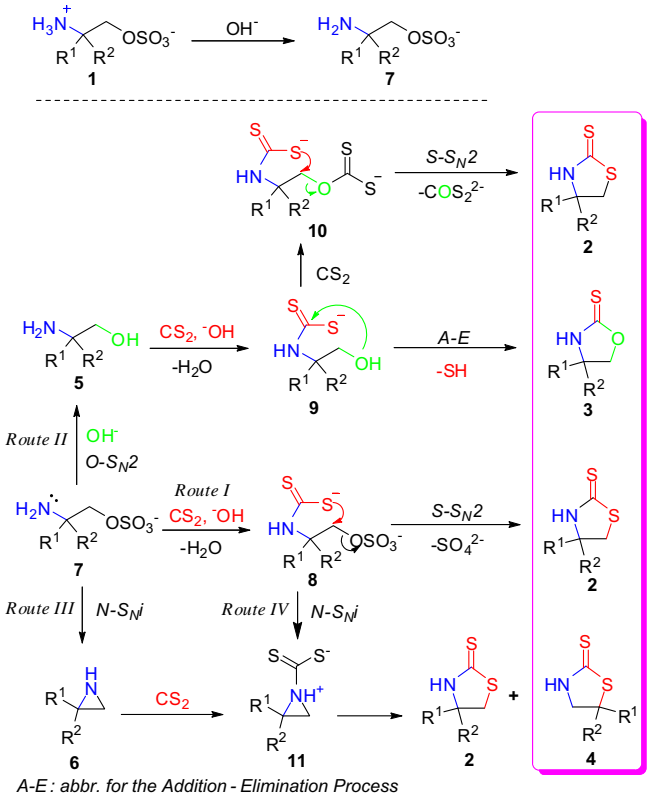
Table 1
Reaction of vicinal amino alcohol hydrogen sulfates **1** and CS_2

Entry	R^1	R^2	**1**	Yield[a] %		
				2	**3**	**4**
1	Me	Me	**1a**	41	31	13
2	Me	Me	**1a**	61	10[b]	20[b]
3	$(CH_2)_6$		**1b**	81	1[b]	10[b]
4	$BnCH_2$	Me	**1c**	80	3[b]	Trace
5	(*S*)-Ph	H	**1d**	91	2[b]	0
6	Ph	Me	**1e**	68	5[b]	24

[a] Isolated yield except for mentioned elsewhere.
[b] NMR yield.



Scheme 1. Reaction of vicinal amino alcohol hydrogen sulfates **1** with CS_2.



Scheme 2. Formation mechanisms of products **2** and **3**, and assumed formation process of product **4** in the reaction of amino alcohol hydrogen sulfates and carbon disulfide.

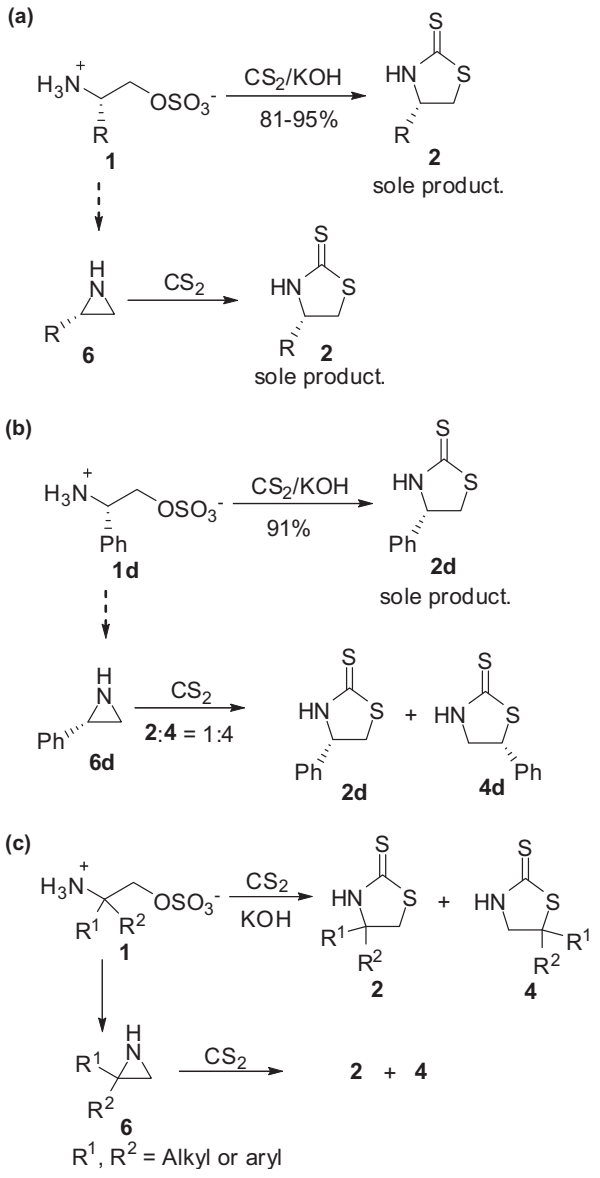
To avoid the formation of 4,4-dimethyloxazolidine-2-thione (**3a**), pure amino alcohol hydrogen sulfate **1a** was prepared via esterification with chlorosulfonic acid and further recrystallization. Purified 2-amino-2-methylpropyl hydrogen sulfate (**1a**) reacted with carbon disulfide under the same conditions (Table 1, entry 2). In the reaction, both products **3a** (yield 10%) and **4a** (yield 20%) were obtained besides **2a** (yield 61%), but the yield of oxazolidine-2-thione **3a** decreased distinctly with a simultaneous increase of thiazolidine-2-thione products (**2a** and **4a**). The similar result was also observed in the reaction of **1b** with carbon disulfide (Table 1, entry 3). However, when 2-amino-2-methyl-4-phenylbutyl hydrogen sulfate (**1c**) (Table 1, entry 4) was applied, only a small amount of 4-methyl-4-phenylethyloxazolidine-2-thione (**3c**) (yield 3%) was generated besides the major product **2c** (yield 80%, Table 1, entry 4).

To improve the yield of the desired products **2**, we then explored the formation mechanism of these products. Vicinal amino alcohol hydrogen sulfates **1** first were neutralized with hydroxide anion to produce free amino alcohol sulfates **7**, which reacted with CS_2 to form the intermediates **8** in the presence of KOH. The sulfur anion in **8** then attacked the carbon atom with the sulfate group to form 4,4-disubstituted thiazolidine-2-thiones **2** (Scheme 2, route I). In the reaction, pure amino alcohol hydrogen sulfates **1** were used. However, **3** were also obtained, indicating that partial hydrogen sulfates **1** hydrolyzed in the basic aqueous solution to generate the free amino alcohols **5**, which underwent further ring-closure with CS_2 to afford oxazolidine-2-thiones **3** and **2** (Scheme 2, route II).[12] The steric hindrance remarkably affects the hydrolysis, further impacting the yield of 4,4-disubstituted oxazolidine-2-thiones **3**. Compound **3a** was obtained in a higher yield (10%) than others since **1a** possesses relatively smaller substituents R^1 and R^2 (methyl) (Table 1, entries 2–6).

The formation of 5,5-disubstituted thiazolidine-2-thiones **4** implied that a rearrangement occurred in this process. We have reported that substituted taurines can be prepared from vicinal amino alcohols by the displacement of their hydrogen sulfates with sodium bisulfite. However, 1-substituted amino ethanols gave rise to 2-substituted taurines via an intramolecular rearrangement through the formation of aziridines as intermediates.[13] Hence, we assumed that vicinal amino alcohol hydrogen sulfates **1** first underwent a Wenker process[14] to form 2,2-disubstituted aziridines **6**. They reacted with CS_2 to generate aziridine-1-carbodithioate intermediates **11**, which further underwent ring-opening regioselectively to give rise to 4,4- and 5,5-disubstituted thiazolidine-2-thiones **2** and **4** (Scheme 2, route III). There is another possibility for the formation of **4**. The intermediates **8** underwent an *N*-S_Ni process instead of the *S*-S_Ni one to generate **11** directly (Scheme 2, route IV). We will identify which of routes III and IV is the formation process of **4**.

It has been reported that 2-monosubstituted 2-amino ethanol hydrogen sulfates reacted with CS_2 to generate 4-substituted thiazolidine-2-thiones as sole products and 1-monosubstituted ones only produced 5-substituted thiazolidine-2-thiones under the same reaction conditions (Scheme 3a).[10] We have also reported that 2-alkylaziridines reacted with CS_2 to only afford 4-substituted thiazolidine-2-thiones, while 2-arylaziridines gave rise to both 4- and 5-arylthiazolidine-2-thiones with a ratio of 1:4 (Scheme 3b).[10]

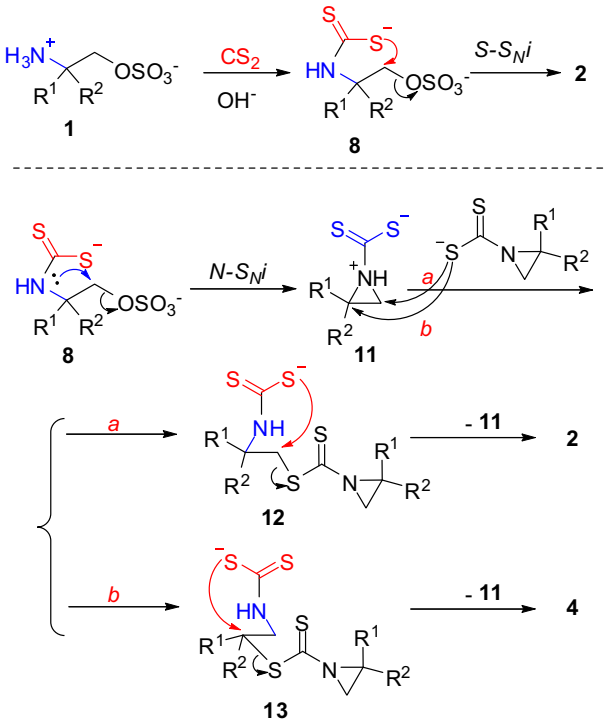
To verify the formation of aziridine derivatives in the reaction, we used pure (*S*)-2-phenylglycinol hydrogen sulfate (**1d**) as starting material to conduct the ring-closure reaction with carbon disulfide (Table 1, entry 5). However, only (*S*)-4-phenylthiazolidine-2-thiones (**2d**) was obtained, demonstrating that no (*S*)-2-phenylaziridine derivative was generated, because if the aziridine was generated, (*R*)-5-phenylthiazolidine-2-thione (**4d**) should have been obtained (Scheme 3b). For 2,2-disubstituted substrates, both 4,4- and 5,5-disubstituted thiazolidine-2-thiones were generated (Table 1, entries 1–4), revealing that 2,2-disubstituted aziridine derivatives



Scheme 3. Reactions of various substituted amino alcohol hydrogen sulfates with carbon disulfide in the presence of potassium hydroxide and reactions of aziridines with carbon disulfide.

were formed (Scheme 3c). It intrigued us to further investigate whether *gem*-disubstituted substrates prefer more obviously the formation of aziridine derivatives as intermediates than monosubstituted substrates.

Both monosubstituted and *gem*-disubstituted vicinal amino ethanol hydrogen sulfates **1** can give rise to the corresponding aziridines under basic condition (the Wenker reaction).[14] However, in the presence of excessive carbon disulfide, aziridine derivatives cannot be generated from monosubstituted vicinal amino alcohol hydrogen sulfates **1**, but can from *gem*-disubstituted ones. On the basis of the observation, we believed that **1** first reacted with carbon disulfide to afford the dithiocarbomate sulfates **8** in the presence of excessive CS_2 and KOH (Scheme 4, also see Scheme 2, route IV), instead of the direct Wenker reaction (Scheme 2, route III). Subsequently, there existed two intramolecular ring-closing pathways between *sulfur*- and *nitrogen*-nucleophilic attacks. If the sulfur anion in **8** worked as the nucleophilic atom, **2** were directly synthesized via the *S*-S_Ni process. Otherwise, the nitrogen atom in **8** attacked the vicinal carbon with the leaving of sulfate group via the *N*-S_Ni process to produce aziridine-1-carbodithioates **11** that were then ring-opened by another molecule of **11** to form intermediates **12** and/or **13**, which further underwent an intramolecular *sulfur*-nucleophilic substitution to afford the final *gem*-disubstituted thiazolidine-2-thiones **2** and **4** (Scheme 4).[10,15] Attempt to determine the existence of aziridine derivatives in the reaction system failed possibly because of their short lifetime under reaction conditions.



Scheme 4. Proposed mechanism in the formation of *gem*-disubstituted thiazolidine-2-thiones in the reaction of amino alcohol hydrogen sulfates and carbon disulfide via aziridine intermediates.

2.2. Thorpe–Ingold effect in the formation of *gem*-disubstituted thiazolidine-2-thiones

In 1915, Thorpe and Ingold first postulated that the mutual repulsion of *gem*-dimethyl groups in an open carbon chain causes an increase in angle β with a simultaneous decrease in angle α.[3] The compression of the internal angle brings the functional groups X and Y closer together and thus promotes the intramolecular cyclization. The postulate was named as the Thorpe–Ingold effect.[1] They reported that the displacement of hydrogen(s) of the ethylene group with the more sterically demanding alkyl groups produces a compression of the internal angle (β). As a result, the two reactive groups X and Y at the end of the system move closer together, and this facilitates the intramolecular cyclization (Fig. 1).

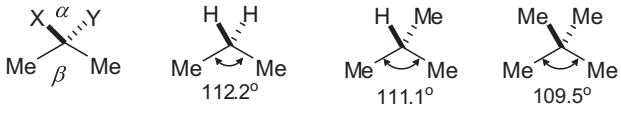


Fig. 1. Thorpe–Ingold effect (angle compression).[12]

In our systems, according to the Thorpe–Ingold effect, *gem*-disubstituted intermediates **8** underwent the ring-closure more favorably than the monosubstituted ones, because their nitrogen atom is closer to their vicinal carbon atom compared with the monosubstituted cases. We calculated all the angles of N–C–C in the intermediates **8** with DFT (the density functional theory) method at

the B3LYP theory level. The angles in disubstituted dithiocarbomates **8** are near 104.0°, while those in monosubstituted and unsubstituted ones are near 107.8° and 109.4°, respectively (Fig. 2). Therefore, the results can rationalize the favorable ring-closing process.

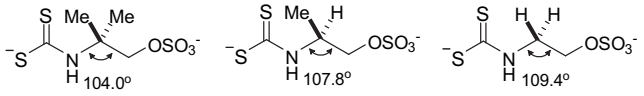


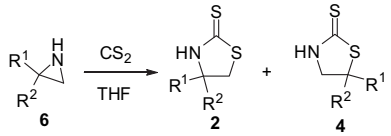
Fig. 2. Thorpe–Ingold effect in intermediates **8** (angle compression).

Further investigation was conducted by introducing an aryl group to the substrates with the hope of increasing the yield of 5,5-disubstituted thiazolidine-2-thiones **4**. 2-Amino-2-phenylpropyl hydrogen sulfate (**1d**), prepared from 2-amino-2-phenylpropanol (**5d**), reacted with carbon disulfide to produce both 4,4- and 5,5-disubstituted thiazolidine-2-thiones (**2d** and **4d**, Table 1, entry 6). Compared with the former ones (**1d**, **2d**, and **3d**, Table 1, entries 2–4), the yield of **4d** increased indeed, indicating that introducing the aryl group to the substituent can benefit for the formation of 5,5-disubstituted thiazolidine-2-thiones **4**. The results demonstrated again that aziridine derivative intermediates were produced during the process.

2.3. Reactions of 2,2-disubstituted aziridines 6 and carbon disulfide

To confirm the formation of aziridine derivatives in the ring-closure process, 2,2-disubstituted aziridines **6** were synthesized via the Wenker reaction and reacted with CS_2 to afford both 4,4- and 5,5-disubstituted thiazolidine-2-thiones **2** and **4** except for 2-methyl-2-phenylethylaziridine (6**c**) (Table 2, entries 1–4). The results revealed that 2,2-disubstituted aziridines were attacked at their tertiary carbon atom to form 5,5-disubstituted thiazolidine-2-thiones **4** (Scheme 5a) and at their less steric carbon to form 4,4-disubstituted ones **2**. The yield of **4d** (44%) was greater than others (**1d**, **2d**, and **3d**) due to the stability of the *p*-π conjugation in the transition state of the ring-opening (Scheme 5b). However, the steric hindrance notably affected the ring-opening process (Scheme 5c). Thus, 4,4-disubstituted thiazolidine-2-thiones **2** were always the major products even though with the aryl substituent (**4d**). The detailed reaction processes are shown in Scheme 5.

Table 2
Reaction of 2,2-disubstituted aziridines **6** and carbon disulfide

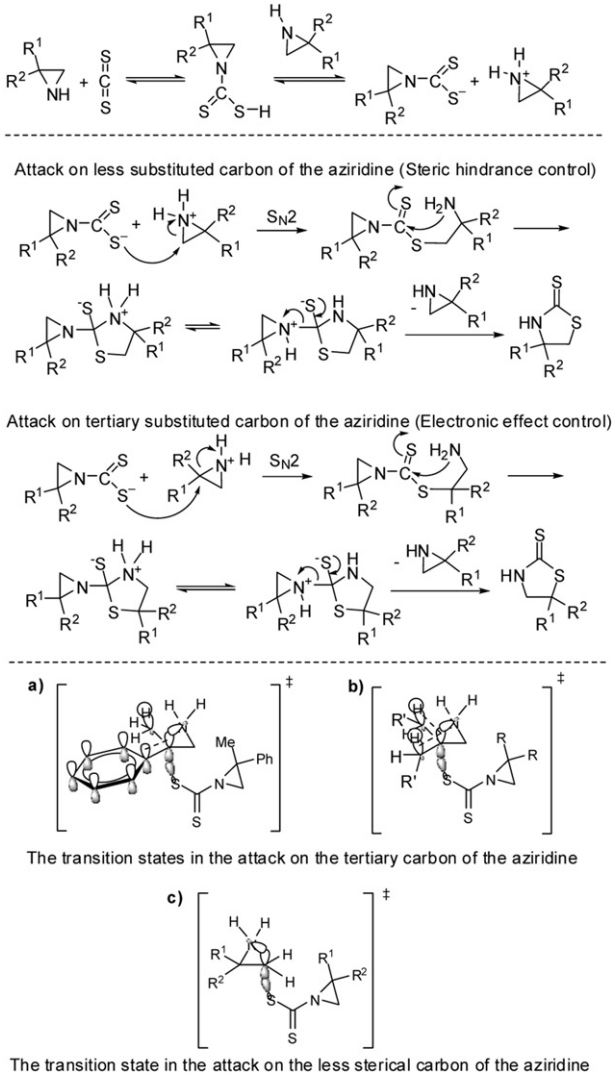


6 **2** **4**

Entry	R^1	R^2	**6**	Yield[a] %	
				2	**4**
1	Me	Me	**6a**	70	20
2	$(CH_2)_6$		**6b**	72	18
3	$BnCH_2$	Me	**6c**	90[b]	Trace
4	Ph	Me	**6e**	54	36

[a] ^1H NMR yield.
[b] Compound **6c** cannot react with CS_2 directly, and the yield was obtained under the catalysis of tetrabutylammonium iodide (TBAI).

Aziridine **6c** cannot react with CS_2 directly without the catalysis of tetrabutylammonium iodide, and **4c** was not observed in its reaction. The results demonstrate that **1c** cannot give rise to **4c** (Table 1, entry 4), not because no aziridine **6c** formed, but because aziridine **6c** cannot generate 5,5-disubstituted thiazolidine-2-thione **4c**.



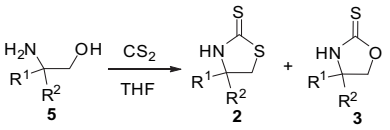
Scheme 5. Reactions of aziridines with carbon disulfide.

2.4. Reactions of 2,2-disubstituted amino ethanols 5 and carbon disulfide

To identify the formation of 4,4-disubstituted oxazolidine-2-thiones **3** from free vicinal amino alcohols generated in the reaction system. 2,2-Disubstituted amino alcohols **5** were used as substrates to react with carbon disulfide directly. To our surprise, after mixing **5a** and CS_2 in KOH aqueous solutions, 4,4-dimethyloxazolidine-2-thione (**3a**) was formed immediately (Table 3, entry 1). We have reported that 4-substituted thiazolidine-2-thiones were synthesized as the sole products from the corresponding amino alcohols **5** and CS_2 under refluxing (16 h),[10] because 4-substituted oxazolidine-2-thiones **3** can slowly convert to the corresponding thiazolidine products **2**.[12] However, when the procedure was applied to the preparation of 4,4-disubstituted thiazolidine-2-thiones **2**, the yields of thiazolidine-2-thiones **2** were relatively poor and 4,4-disubstituted oxazolidine-2-thiones **3** became the major products (Table 3, entries 2–6). We hoped to improve the yield of **2a** by prolonging the reaction time. However, the yield decreased after refluxing for 72 h (Table 3, entries 2 and 3). No **2a** was generated in the reaction of 4,4-dimethyloxazolidine-2-thione (**3a**) with CS_2 in sodium hydroxide solution, indicating that 4,4-disubstituted oxazolidine-2-thiones **3** cannot be converted into the corresponding 4,4-disubstituted thiazolidine-2-thiones **2**. For

further investigation, other substrates **5b**, **5c**, and **5e** were tested. In each of cases, thiazolidine-2-thiones (**2b**, **2c**, and **2e**) were obtained in poor yields and the corresponding oxazolidine-2-thiones **3** were always the major products (Table 3, entries 4–6). The results reveal that the steric hindrance affects yields significantly because the intermediates **9** can hardly further react with carbon disulfide to generate the key intermediates **10** (Scheme 2, route II), and the yield of thiazolidine-2-thiones **2** decreased while that of oxazolidine-2-thiones **3** increased.

Table 3
Reaction of 2,2-disubstituted amino ethanols **5** and carbon disulfide



Entry	R^1	R^2	5	Yield[a] %	
				2	3
1	Me	Me	**5a**	67[b]	0
2	Me	Me	**5a**	41	43
3	Me	Me	**5a**	38[c]	36
4	$(CH_2)_6$		**5b**	19	79
5	$BnCH_2$	Me	**5c**	36	63
6	Ph	Me	**5e**	11	81

[a] All of reactions were conducted under refluxing in an oil bath at 110 °C for 16 h except for mentioned elsewhere, and the yields were isolated yields.
[b] The reaction was conducted at room temperature for 1 h.
[c] The reaction was conducted under refluxing for 72 h.

3. Conclusion

The Thorpe–Ingold effect is the key factor that remarkably affects the ring-closure rates and efficiency and even further influences the structures of products in some cases. The reaction of vicinal tertiary amino primary alcohol hydrogen sulfates and carbon disulfide in the presence of potassium hydroxide produced not only the desired 4,4-disubstituted thiazolidine-2-thiones, but also their isomers 5,5-disubstituted thiazolidine-2-thiones via 2,2-disubstituted aziridine-1-carbodithioate intermediates generated in the reaction due to the Thorpe–Ingold effect, as well as their oxygen analogues 4,4-disubstituted oxazolidine-2-thiones formed from free amino alcohols, which were yielded via basic hydrolysis of amino alcohol hydrogen sulfates in the reaction system. The current results indicate that the Thorpe–Ingold effect is an important factor that can regulate chemo- and regioselectivities in the ring-closure reactions via its impact on the ring-closure rates and efficiency of different nucleophiles in reactants.

4. Experimental section

4.1. General

Melting points were determined on a melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz in $CDCl_3$ with TMS as the internal standard. ^{13}C NMR spectra were recorded at 50.3, 75.5, or 100.6 MHz in $CDCl_3$ with $CDCl_3$ as the internal standard at 77.0 ppm. IR spectra were determined directly. MS spectra were obtained on an ESI mass spectrometer. HRMS spectra were performed on an LC/MSD TOF mass spectrometer.

4.2. General procedure for the reaction of vicinal amino alcohol hydrogen sulfates 1 and carbon disulfide[10]

Under the mechanical stirring, chlorosulfonic acid (0.4 mL, 0.7 g, 12 mmol) was added dropwise to a solution of amino alcohol (5 mmol) in anhydrous acetonitrile (25–50 mL) in an ice-water bath. The resulting mixture was stirred for 1 h. The precipitates were filtrated and washed with ethanol twice and diethyl ether twice to afford solid amino alcohol hydrogen sulfate **5**, which was further purified via recrystallization from ethanol.

To a mixture of the prepared amino alcohol hydrogen sulfate (1 mmol) and carbon disulfide (0.25 mL, 0.31 g, 4 mmol) was added 0.65 mL of 6.2 mol/L KOH aqueous solution. The resulting solution was refluxed at 80 °C in an oil bath for 3.5 h. After cooling to room temperature, to the reaction mixture was added 10 mL of water and then was extracted with dichloromethane (3×10 mL). The combined organic layer was dried over Na_2SO_4. Removal of the solvent thoroughly under reduced pressure gave a crude product. After purified via recrystallization or via silica gel column chromatography eluented with petroleum ether (60–90 °C)/ethyl acetate (2:1, v/v), colorless crystals were obtained.

4.3. General procedure for the reaction of amino alcohols 5 and carbon disulfide[12]

To a mixture of an amino alcohol (1 mmol) in 5 mL of 1 mol/L KOH aqueous solution was added carbon disulfide (0.31 mL, 0.38 g, 5 mmol). The resulting solution was refluxed at 100 °C in an oil bath for 16 h. After cooling to room temperature, to the reaction mixture was added 10 mL of water and then was extracted with dichloromethane (3×10 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed thoroughly under reduced pressure to give a crude product. After purified via silica gel column chromatography eluented with petroleum ether (60–90 °C)/ethyl acetate (2:1, v/v), disubstituted thiazolidine-2-thione and oxalidine-2-thiones were obtained as colorless crystals.

4.4. General procedure for the reaction of aziridines and carbon disulfide[15]

To a mixture of an aziridines (1 mmol) in 5 mL of anhydrous THF was added carbon disulfide (0.26 mL, 304 mg, 4 mmol). The resulting solution was refluxed at 80 °C in an oil bath for 1 h. If no reaction, tetrabutylammonium iodide (18 mg, 5%) was added as the catalyst. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure. After purified via recrystallization or via silica gel column chromatography eluented with petroleum ether (60–90 °C)/ethyl acetate, thiazolidine-2-thiones were obtained as colorless crystals.

*4.4.1. 4,4-Dimethylthiazolidine-2-thione (**2a**)[10].* Colorless crystals, yield: 61%. Mp 124–126 °C. Lit.[5] mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.87 (br s, 1H, NH), 3.34 (s, 2H, CH_2S), 1.51 (s, 6H, $2CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 198.5, 67.7, 45.6, 26.7.

*4.4.2. 3-Thia-1-azaspiro[4.6]undecane-2-thione (**2b**)[10].* Colorless crystals, yield: 81%. Mp 156–158 °C. Lit.[5] mp 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (br s, 1H, NH), 3.30 (s, 2H, CH_2S), 2.01–1.89 (m, 4H, $2CH_2CN$), 1.62–1.45 (m, 8H, $4CH_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 198.3, 74.3, 44.9, 38.8, 29.4, 22.9.

*4.4.3. 4-Methyl-4-phenethylthiazolidine-2-thione (**2c**)[10].* Colorless crystals, yield: 80%. Mp 143–145 °C. Lit.[5] mp 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.78 (br s, 1H, NH), 7.32–7.26 (m, 2H, ArH), 7.22–7.17 (m, 3H, ArH), 3.44 (d, J=11.1 Hz, 1H in CH_2S), 3.24 (d, J=11.1 Hz, 1H in CH_2S), 2.75–2.69 (m, 2H, CH_2Ar), 2.09–2.02 (m, 2H, CH_2CN), 1.52 (s, 3H, Me). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 198.9, 140.4, 128.6, 128.2, 126.3, 70.3, 43.7, 41.7, 30.6, 25.3.

*4.4.4. 4-Methyl-4-phenylthiazolidine-2-thione (**2e**).* Colorless crystals, yield: 68%. Mp 140–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64

(s, 1H), 3.64 (d, J=11.2 Hz, 1H), 3.62 (d, J=11.2 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.1, 142.4, 129.0, 128.3, 124.7, 72.1, 47.6, 26.5. IR ($CDCl_3$) ν (cm^{-1}): 3131 (NH), 1494 (N–C=S). HRMS (ESI, m/z): calcd for $C_{10}H_{12}NS_2$ $[M+H]^+$: 210.0406. Found 210.0409.

*4.4.5. 4,4-Dimethylthiazolidine-2-thione (**3a**).* Colorless crystals, yield: 67%. Mp 125–128 °C. Lit.[16] mp 124.6–125.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (br s, 1H, NH), 4.35 (s, 2H, CH_2O), 1.44 (s, 6H, $2CH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 188.3, 81.7, 60.2, 26.8. IR (CH_2Cl_2), ν (cm^{-1}): 3149 (NH), 1490 (N–C=S).

*4.4.6. 3-Oxa-1-azaspiro[4.6]undecane-2-thione (**3b**).* Colorless crystals, yield, 79%. Mp 110–112 °C. R_f=0.20 (PE/EA=4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.28 (br s, 1H, NH), 4.34 (s, 2H, CH_2), 1.98–1.80 (m, 4H, $2CH_2CN$), 1.66–1.45 (m, 8H, $4CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 187.7, 81.3, 66.6, 39.0, 28.7, 22.2. IR (CH_2Cl_2), ν (cm^{-1}): 3152 (NH), 1491 (N–C=S). MS (ESI, m/z): 186.0 $[M+H]^+$, 208.0 $[M+Na]^+$. HRMS (ESI, m/z): calcd for $C_9H_{16}NOS$ $[M+H]^+$: 186.0947. Found 186.0952.

*4.4.7. 4-Methyl-4-phenylethylthiazolidine-2-thione (**3c**).* Colorless crystals, yield: 63%. Mp 143–145 °C. R_f=0.46 (PE/EA=2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.91 (br s, 1H, NH), 7.31 (m, 2H, ArH_{meta}), 7.18 (m, 3H, $ArH_{ortho-para}$), 4.42 (d, J=9.0 Hz, 1H in CH_2S, AB system), 4.29 (d, J=9.0 Hz, 1H in CH_2S, AB system), 2.68 (m, 2H, CH_2Ar), 1.96 (m, 2H, CH_2C), 1.46 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 188.4, 140.2, 128.6, 128.2, 126.3, 80.2, 62.9, 41.6, 30.2, 25.2. IR ($CDCl_3$) ν (cm^{-1}): 3138 (NH), 1490 (N–C=S). MS (ESI, m/z): 222.0 $[M+H]^+$. HRMS (ESI, m/z): calcd for $C_{12}H_{16}NOS$ $[M+H]^+$: 222.0947. Found 222.0946.

*4.4.8. 4-Methyl-4-phenyloxazolidine-2-thione (**3e**).* Colorless crystals, yield: 81%. Mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (s, 1H, NH), 7.45–7.31 (m, 5H, ArH), 4.63 (d, J=8.8 Hz, 1H), 4.60 (d, J=8.8 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 189.2, 141.9, 129.2, 128.4, 124.7, 83.1, 65.1, 26.6. IR ($CDCl_3$) ν (cm^{-1}): 3142 (NH), 1493 (N–C=S). HRMS (ESI, m/z): calcd for $C_{10}H_{12}NOS$ $[M+H]^+$: 194.0634. Found 194.0633.

*4.4.9. 5,5-Dimethylthiazolidine-2-thione (**4a**)*[17]. Colorless crystals, yield: 20%. Mp 110–112 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.40 (br s, 1H, NH), 3.70 (s, 2H, CH_2N), 1.59 (s, 6H, 2 Me). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 201.5, 63.5, 56.9, 28.0. IR ($CDCl_3$) ν (cm^{-1}): 3151 (NH), 1491 (N–C=S).

*4.4.10. 1-Thia-3-azaspiro[4.6]undecane-2-thione (**4b**).* Colorless crystals, yield: 10%. Mp 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (s, 1H), 3.68 (s, 2H), 2.18 (dd, J=14.3, 6.7 Hz, 1H), 1.93 (dd, J=14.5, 8.6 Hz, 2H), 1.61 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.6, 66.1, 62.9, 40.1, 28.0, 24.0. IR ($CDCl_3$) ν (cm^{-1}): 3150 (NH), 1496 (N–C=S). HRMS (ESI, m/z): calcd for $C_9H_{16}NS_2$ $[M+H]^+$: 202.0718. Found 202.0705.

*4.4.11. 5-Methyl-5-phenylthiazolidine-2-thione (**4e**).* Colorless crystals, yield: 24%. Mp 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 4.23 (d, J=11.2 Hz, 1H), 3.93 (d, J=11.2 Hz, 1H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.8, 141.6, 128.9, 128.1, 126.0, 63.6, 62.9, 29.1. IR ($CDCl_3$) ν (cm^{-1}): 3151 (NH), 1491 (N–C=S). HRMS (ESI, m/z): calcd for $C_{10}H_{12}NS_2$ $[M+H]^+$: 210.0406. Found 210.0401.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.08.023. These data include MOL files and InChiKeys of the most important compounds described in this article.

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