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A mild cyclodesulfurization of *N*-(2-hydroxyethyl)-*N′*-phenylthioureas to 2-phenylamino-2-oxazolines using TsCl/NaOH

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Abstract—An efficient synthesis of 2-phenylamino-2-oxazolines **3** via cyclodesulfurization of *N*-(2-hydroxyethyl)-*N′*-phenylthioureas **2** by a one-pot reaction using *p*-toluenesulfonyl chloride (TsCl) and NaOH in very good yields is described.

1. Introduction

2-Amino-2-oxazolines are of particular interest as biological active molecules such as a potent adrenoceptor agonist,[1] imidazoline receptor agonist,[2] and octopaminergic agonist.[3] This interest has stimulated considerable research in the preparation of a variety of compounds. 2-Amino-2-oxazolines are generally prepared by the following methods: the cyclization of *N*-(2-haloethyl)ureas[1a,4] or *N*-(2-hydroxyethyl)guanidine,[5] the ring opening of aziridines with isocyanates,[6] the reaction between 2-aminoalcohol and cyano bromide,[7] the cyclization of *N*-(2-hydroxyethyl)thiopseudoureas with sodium ethoxide in reflux,[5a,8] and the cyclodesulfurization of *N*-(2-hydroxyethyl)thioureas with mercuric oxide[9] or superoxide radical anion.[10] Each method has its advantages and disadvantages in any given situation, therefore, no one reagent has proven totally general. Thus, the development of other methods is necessary.

Recently we reported that 2-phenylamino-2-thiazolines **4** were synthesized by the selective *S*-cyclization of *N*-(2-hydroxyethyl)-*N′*-phenythioureas **2** using TsCl and NaOH.[11a] During the course of our development of a new chiral auxiliary using a chiral 2-phenylamino-2-thiazoline prepared according to this procedure (TsCl/NaOH), we found that this compound contained no sulfur atom in elemental analysis. Thus, the previous report has the wrongly proposed structure,[11] prompting us to embark on the detailed cyclization reaction of *N*-(2-hydoxyethyl)-*N′*-phenylthioureas **2** under TsCl/NaOH and corrections of misassigned structures. The cyclization of *N*-(2-hydroxyethyl)thioamides system with TsCl in the presence of triethylamine resulted in the formation of thiazolines as cyclodehydration products.[12] In this article, we report that the cyclization of *N*-(2-hydoxyethyl)thioureas **2** with TsCl results in the oxazolines as cyclodesulfurization products as well as thiazolines depending on *N*-substituents.

2. Results and discussion

The starting *N*-(2-hydroxyethyl)thioureas **2** were readily obtained in high yields from the reaction of the corresponding 1,2-aminoalcohols with phenyl isothiocyanate, which provided exclusively the desired products under mild conditions, thus avoiding the need for O-protection.[11] First investigations of one-pot reactions of both **2a** and **2f** by the combination of TsCl (1.1 equiv.) with various basic metallic (*t*-BuOK, NaOH, and NaH) or non-metallic (Et_3N and Et_3N/DMAP) reagents were performed in THF (Table 1). Among them, the use of NaOH was found to be most effective in producing cyclization products (entry 2). Compound **2f** due to a *gem*-dimethyl effect cyclized quickly offering **3f** in high yields.[13] With **2a**, the cyclization did not occur in some conditions (entries 3–6) yielding the tosylated product. The structure of 2-oxazoline **3f** was wrongly proposed to *S*-cyclization product such as 2-thiazoline in our previous report, assigning the peak at δ 4.02 to the –N=C–SCH_2– proton in NMR.[11]

The cyclization of various substrates **2a**–**2i** using 1.1 equiv. of TsCl and 2.5 equiv. of NaOH was performed at room temperature and the results are shown in Table 2. With thiourea **2a**–**2f** prepared from N-unsubstituted aminoalcohols (R^3=H), 2-phenylamino-2-oxazolines **3a**–**3f**

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Table 1. Effect of base in one-pot reaction of **2a** and **2f**

Entry	Base	Time, temperature	Yield %[a,b] of **3a**	Yield %[a,b] of **3f**
1	*t*-BuOK (2.5 equiv.)	30 min, 0°C	37 (13)	78
2	NaOH (2.5 equiv.)	30 min, rt	64 (6)	94
3	NaH (2.5 equiv.)	30 min, rt	– (11)	62 (10)
4	Et_3N (5.0 equiv.)	17 h, reflux	– (44)	62
5	Et_3N/DMAP (5.0/0.5 equiv.)	17 h, reflux	– (33)	[c]

[a] Isolated yields by column chromatography.
[b] Parenthesis is the isolated tosylate yield and the position of tosylation was not determined.
[c] Not tested.

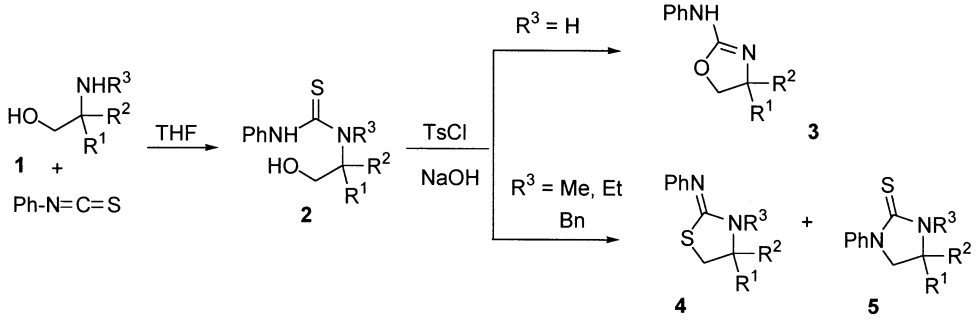
Table 2. Cyclization of *N*-(2-hydroxyethyl)-*N*-phenylthioureas **2**

Entry	Substrate	R^1	R^2	R^3	Product	Yield %[a]
1	**2a**	H	H	H	**3a**	64
2	**2b**	Me	H	H	**3b**	77
3	**2c**	Et	H	H	**3c**	78
4	**2d**	(*S*)-$PhCH_2$	H	H	**3d**	90
5	**2e**	(*S*)-*i*-Pr	H	H	**3e**	85
6	**2f**	Me	Me	H	**3f**	94
7	**2g**	H	H	Me	**4g/5g**	29/54[b]
8	**2h**	H	H	Et	**4h/5h**	27/65[b]
9	**2i**	H	H	$PhCH_2$	**4i/5i**	18/50[b]

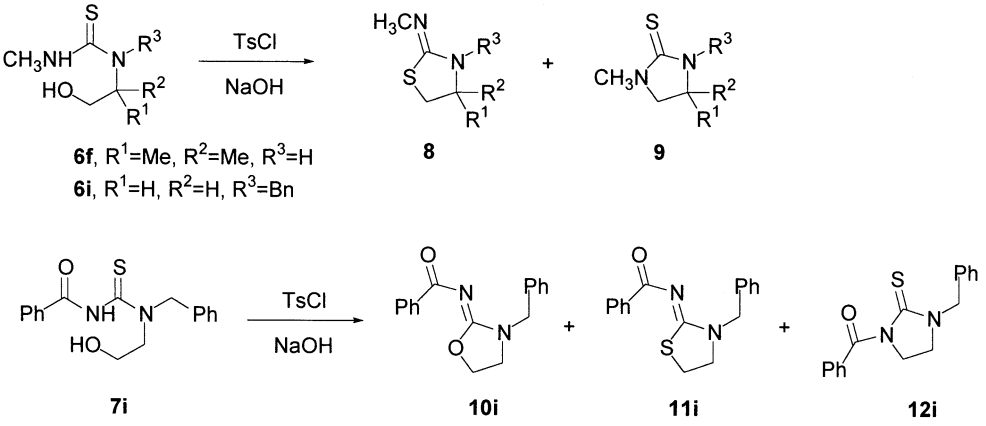
[a] Isolated yields by column chromatography.
[b] The ratio of the crude mixtures determined by ^1H NMR was as follows: 43/57 in **4g/5g**, 30/70 in **4h/5h**, and 31/69 in **4i/5i**.

through *O*-cyclization were regioselectively obtained (entires 1–6) and only **2a** gave the tosylated products in 6% yield as a by-product (Scheme 1). All 2-oxazolines were identified with spectroscopic data, elemental analysis, and the comparison of authentic sample data.[4,5a] In contrast, the thioureas **2g–2i** prepared from *N*-substituted aminoalchols (R^3=Me, Et, Bn) gave a cyclodehydrated mixture of 2-iminothiazolines (*S*-cyclization products) **4g–4i** and 2-imidazolidinethiones (*N*-cyclization products) **5g–5h** without the 2-oxazolines (entries 7–9).[14,15] It is noteworthy in the above reactions to note that the ring closure of the substrates **2a–2f** having *N*-unsubstituents using TsCl/NaOH proceeded through the cyclodesulfurization to provide regiocontrolled 2-phenylamino-2-oxazolines.[16]

Next, we were interested to see if the related selective transformation could be effected on a variety of thioureas derived from the alkyl isothiocyanate and benzoyl isothiocyanate to figure out the scope and limitations of this synthetic methodology (Scheme 2). Thus, cyclization of the *N*-methylthioureas such as **6f** and **6i** was performed to produce along with a mixture of the *S*- and *N*-cyclization in the proton NMR ratios of 92/8 and 70/30, respectively.



Scheme 1.



Scheme 2.

Compared to **2f**, the cyclization of **6f** yielded the mixture of S- and N-alkylation products without the oxazoline. Cyclization of **7i** derived from benzoyl isothiocyanate led to the mixture of the O-(60%) and *N*-cyclized product (15%) with trace amount of *S*-cyclized product (5%). Benzoyl substituted **7i** having *N*-substituted benzyl group, compared to **2i**, provided the oxazoline as a main product to be considered to proceed via S-tosylation. That is, **6f** and **7i** gave totally different mixtures from *N*-phenylthiourea **3**. Thus, we abandoned any further efforts to establish the generality of this transformation.

The exact mechanistic explanation of this study remains unclear at the present time. The ratio, however, of O-, N-, and *S*-cyclized products seems to depend on the acidity of the thiourea moiety and steric hindrance around the sulfur atom. The substrate having more acidic thiourea moiety (PhCONH>PhNH>MeNH) and the less hindered sulfur atom (N-unsubstituted>*N*-substituted) tends to undergo *O*-cyclization rather than N- and *S*-cyclization via S-tosylation, giving the 2-oxazoline derivative mainly.

In conclusion, the right closure of *N*-(2-hydroxyethyl)-*N′*-phenylthioureas **2** is proven to furnish 2-pheylamino-2-oxazolines **3** as well as 2-phenylamino-2-thiazolines **4** and 2-imidazolidinethiones **5** depending on the substituent of thioureas. We have found a new entry to the synthesis of 2-phenylamino-2-oxazolines by a mild one-pot cyclization of *N*-(2-hydroxyethyl)-*N′*-phenylthioureas prepared from N-unsubstituted 1,2-aminoalcohols and phenyl isothiocyanate. We believe that this methodology will be applicable to the combinatorial approach to 2-arylamino-2-oxazolines, which is expected to have biological activities as mentioned above. Additionally, chiral 2-phenylamino-2-oxazoline like **3d** and **3e** may be applicable to chiral auxiliaries as an Evans-type of 2-oxazolidione.[17]

3. Experimental

3.1. General

^{1}H- and ^{13}C NMR spectra were recorded using 300 and 75 MHz NMR spectrometer; chemical shifts are reported in ppm using TMS as an internal standard. Melting points were measured in a glass capillary apparatus and uncorrected. Mass spectra were recorded on a HP 5983B GC/Mass spectrometer. Elemental analysis was performed in the Korea Basic Science Institute, Kwangju, Korea. Analytical TLC was performed on 0.25 mm precoated silica gel plates. Flash chromatography was carried out with 230–400 mesh silica gel.

3.2. Cyclization of *N*-(2-hydroxyethyl)thioureas

To a stirred solution of thiourea (0.88 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of NaOH (88 mg, 2.2 mmol, 250 M%) in water (3 mL) and TsCl (0.18 g, 0.97 mmol, 110 M%) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min at room temperature, quenched with water (30 mL), and extracted with ether (50 mL×3). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give the cyclized product.

3.2.1. 4,5-Dihydro-*N*-phenyl-2-oxazolamine (3a). White solid, mp 121–123°C (lit.[5a] mp 119–120°C); R_f=0.2 (ethyl acetate); ^{1}H NMR ($CDCI_3$) δ 7.24–7.26 (4H, m), 6.94–7.00 (1H, m), 4.36 (2H, t, J=8.2 Hz), 3.81 (2H, t, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 157.9, 141.4, 128.9, 122.2, 119.7, 67.4, 49.8. Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 67.10; H, 6.39; N, 17.75.

3.2.2. 4,5-Dihydro-4-methyl-*N*-phenyl-2-oxazolamine (3b). White solid, mp 108–110°C (lit.[4] mp 111°C); R_f=0.3(ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1687; ^{1}H NMR ($CDCl_3$) δ 7.20–7.28 (4H, m), 6.94–7.00 (1H, m), 4.43 (1H,t, J=8.0 Hz), 4.10–4.17 (1H, M), 3.87 (1H,t, J=7.5 Hz), 1.27 (3H, d, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 156.8, 142.8, 128.8, 122.2, 120.4, 73.6, 55.3, 21.2. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.35; H, 6.67; N, 16.41.

3.2.3. 4,5-Dihydro-4-ethyl-*N*-phenyl-2-oxazolamine (3c). White solid, mp 100–102°C (lit. [5a] mp 100–101°C); R_f=0.2 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1703; ^{1}H NMR ($CDCl_3$) δ 7.13–7.29 (4H, m), 6.94–7.03 (1H, m), 4.37–4.43 (1H, m), 3.88–3.99 (2H, m), 1.49–1.67 (2H, m), 0.93 (3H, t. J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 156.8, 143.1, 128.7, 122.1, 120.6, 71.9, 60.8, 28.5, 9.7. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.82; H, 7.75; N, 15.16.

3.2.4. (4*S*)-4,5-Dihydro-*N*-phenyl-4-phenylmethyl-2-oxazolamine (3d). Colorless oil, R_f=0.3 (ethyl acetate/hexane 1:1); $[\alpha]^{20}_D$=+3.6 ($CHCl_3$, c=0.7); IR ($CDCl_3$, cm^{-1}) 1687 ^{1}H NMR ($CDCl_3$) δ 7.19–7.33 (9H, m), 6.95–6.99 (1H, m), 4.25–4.30 (2H, m), 4.13–4.04 (1H, m), 3.00 (1H, dd, J=5.2, 13.5 Hz), 2.73 (1H, dd, J=7.4, 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 157.8, 143.1, 138.5, 130.1, 129.7, 129.5, 127.5 123.2, 120.9, 72.4, 63.0, 42.9. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.35; H, 6.74; N, 11.40.

3.2.5. (4*S*)-4,5-Dihydro-4-(1-methylethyl)-*N*-phenyl-2-oxazolamine (3e). White solid, mp 65–67°C; R_f=0.3 (ethyl acetate/hexane 1:1) $[\alpha]^{20}_D$=+3.1 ($CHCl_3$, c=0.8); IR ($CDCl_3$, cm^{-1}) 1680; ^{1}H NMR ($CDCl_3$) δ 7.19–7.27 (4H, m), 6.94–6.99 (1H, m), 4.28 (1H, dd, J=8.2, 8.2 Hz), 3.99 (1H, dd, J=6.6, 8.2 Hz), 3.64–3.71 (1H, m) 1.60–1.71 (1H, m), 0.88 (3H, d, J=6.7 Hz), 0.81 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 156.9, 143.3, 128.8, 122.2, 120.8, 70.3, 65.1, 33.1, 18.7, 18.0. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 71.01; H, 7.45; N, 13.52.

3.2.6. 4,5-Dihydro-4,4-dimethyl-*N*-phenyl-2-oxazolamine (3f). White solid, mp 115–116°C (lit.[5a] mp 114–116°C); R_f=0.3 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1687; ^{1}H NMR ($CDCl_3$) δ 7.14–7.27 (4H, m), 6.93–7.00 (1H, m), 4.02 (2H, s), 1.33 (6H, s); ^{13}C NMR ($CDCl_3$) δ 157.7, 142.4, 128.8, 122.1, 120.4, 78.6, 61.9, 28.0. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.80; H, 7.72; N, 15.04.

3.2.7. 3-Methyl-2-phenyliminothiazolidine (4g). White solid, mp 88–89°C (lit.[9a] mp 89°C); R_f=0.4 (ethyl acetate/

hexane/dichloromethane 1:1:1); IR ($CDCl_3$, cm^{-1}) 1616, 1576; ^1H NMR ($CDCl_3$) δ 6.92–7.29 (5H, m), 3.56 (2H, t, J=6.8 Hz), 3.13 (2H, t, J=6.8 Hz), 3.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 159.4, 152.4, 128.8, 123.0, 122.1, 53.0, 33.8, 26.8; EIMS *m/z* 57 (55), 71 (25), 149 (100), 167 (46), 192 (M, 32). Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.90 H, 6.23; N, 14.99; S, 16.35.

3.2.8. 1-Methyl-3-phenyl-2-imidazolidinethione (5g). White solid, mp 90–92°C; R_f=0.6 (ethyl acetate/hexane/dichloromethane 1:1:1) IR ($CDCl_3$, cm^{-1}) 1336; ^1H NMR ($CDCl_3$) δ 7.21–7.54 (5H, m), 4.01 (2H, t), 3.73 (2H, t), 3.24 (3H, s); ^{13}C NMR ($CDCl_3$) δ 182.0, 141.0, 128.7, 126.1, 124.8, 48.7, 48.5, 35.2; EIMS *m/z* 51 (54), 57 (60), 77 (100), 91 (38), 192 (M, 11). Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.69; H, 6.64; N, 15.01; S, 17.01.

3.2.9. 3-Ethyl-2-phenyliminothiazolidine (4h). Pale yellow oil, R_f=0.5 (ethyl acetate/hexane 3:7); IR ($CDCl_3$, cm^{-1}) 1624, 1585; ^1H NMR ($CDCl_3$) δ 6.91–7.28 (5H, m), 3.58 (2H, t, J=6.9 Hz), 3.57 (2H, q, J=7.2 Hz), 3.10 (2H, t, J=6.9 Hz), 1.22 (3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 158.4, 152.4, 128.7, 122.8, 126.0, 124.9, 50.2, 41.1, 26.7, 11.9; EIMS *m/z* 51 (45), 56 (57), 77 (100), 206 (M, 1). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.54; H, 6.74; N, 13.20; S, 15.01.

3.2.10. 1-Ethyl-3-phenyl-2-imidazolidinethione (5h). White solid, mp 65–67°C (lit.[19] mp 69°C); R_f=0.4 (ethyl acetate/hexane 3:7); IR ($CDCl_3$, cm^{-1}) 1346; ^1H NMR ($CDCl_3$) δ 7.19–7.55 (5H, m), 3.94–4.00 (2H, m), 3.78 (2H, q, J=7.2 Hz), 3.65–3.72(2H, m), 1.23 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 181.1, 140.9, 128.6, 126.0, 124.9, 48.8, 45.5, 42.4, 11.8; EIMS *m/z* 51 (45), 77 (100), 106 (97), 206 (M, 91). HRMS (EI) Calcd for $C_{11}H_{14}N_2S$ 206.0878, Found 206.0875.

3.2.11. 3-Phenylmethyl-2-phenyliminothiazolidine (4i). White solid, mp 93–95°C (lit.[14] mp 92–94°C); R_f=0.8 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 7H), 7.04–6.97 (m, 3H), 4.71 (s, 2H), 3.49–3.44 (m, 2H), 3.10–3.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 159.0, 152.2, 137.2, 128.8, 128.6, 128.2, 127.4, 123.0, 122.0, 50.2, 50.1, 26.8; EIMS *m/z* 77.1 (57.6), 91.1 (100), 207.2 (32.7), 268.3 (44.7, M). Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.26; H, 5.88; N, 10.34; S, 11.74.

3.2.12. 1-Phenyl-3-phenylmethyl-2-imidazolidinethione (5i). White solid, mp 119–121°C (lit.[14] mp 125–126°C); R_f=0.7 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 7.56–7.53 (m, 2H), 7.43–7.25 (m, 8H), 4.95 (s, 2H), 4.00–3.94 (m, 2H), 3.59–3.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 181.7, 140.9, 136.2, 129.0, 128.3, 127.6, 126.2, 124.9, 51.7, 48.8, 45.6; EIMS *m/z* 77.1 (51.4), 91.1 (100), 136.0 (32.1), 148.0 (34.9), 182.1 (14.2), 239.2 (9.8), 268.2 (29.4, M). Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.15; H, 5.90; N, 10.06; S, 11.50.

3.2.13. 4,5-Dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine (8f). Yield 90%; colorless oil, R_f=0.2 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) 3.26 (2H, s), 2.94 (3H, s), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 28.28, 31.38, 46.16, 73.11, 159.43; Anal. Calcd for $C_6H_{12}N_2S$: C, 49.96; H, 8.39; N, 19.42; S, 22.23. Found: C, 51.22; H, 8.51; N, 19.00; S, 21.85.

3.2.14. 3-Phenylmethyl-2-methyliminothiazolidine (8i). Yield 35%; colorless oil, R_f=0.5 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.32–7.25 (m, 5H), 4.50 (s, 2H), 3.34–3.29 (m, 2H), 3.12–3.07 (m, 2H), 3.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.2, 137.7, 128.5, 128.0, 127.2, 50.3, 50.2, 41.4, 26.7; EIMS *m/z* 43.2 (74.5), 74.9 (100), 90.9 (89.9), 177.9 (43.5), 206.0 (58.7, M). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.83; H, 6.68; N, 13.42; S, 15.12.

3.2.15. 1-Methyl-3-phenylmethyl-2-imidazolidinethione (9i). Yield 18%; pale yellow solid, mp 109–111°C; R_f= 0.8 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.34–7.27 (m, 5H), 4.84 (s, 2H), 3.57–3.50 (m, 2H), 3.43–3.37 (m, 2H), 3.19 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.2, 136.5, 128.6, 128.2, 127.6, 51.8, 48.3, 45.4, 35.1; EIMS *m/z* 44.2 (88.7), 65.1 (73.2), 91.0 (100), 115.0 (34.6), 145.1 (30.1), 206.1 (74.3, M). Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.90; H, 6.79; N, 13.10; S, 15.20.

3.2.16. 3-Phenylmethyl-2-benzoyliminooxazolidine (10i). Yield 60%; white solid, mp 83–84°C; R_f=0.1 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 8.25–8.22 (m, 2H), 7.47–7.32 (m, 8H), 4.68 (s, 2H), 4.55–4.49 (m, 2H), 3.50–3.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.0, 159.7, 137.2, 135.3, 131.6, 129.7, 128.9, 128.3, 128.2, 127.9, 65.8, 49.1, 44.3; EIMS *m/z* 77.1 (75.7), 91.1 (100), 105.1 (73.0), 132.1 (25.5), 175.2 (17.9), 280.3 (13.9, M). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.83; H, 5.63; N, 9.66.

3.2.17. 3-Phenylmethyl-2-benzoyliminothiazolidine (11i). Yield 5%; white solid, mp 122–124°C; R_f=0.5 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 8.33–8.30 (m, 2H), 7.50–7.34 (m, 8H), 5.00 (s, 2H), 3.62–3.57 (m, 2H), 3.18–3.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.9, 172.2, 136.7, 135.8, 131.9, 129.7, 128.9, 128.2, 128.0, 51.2, 48.8, 26.9; EIMS *m/z* 77.1 (100), 91.1 (62.1), 105.1 (75.1), 191.2 (17.9), 296.4 (8.1, M). Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.47; H, 5.47; N, 9.2; S, 10.48.

3.2.18. 1-Benzoyl-3-phenylmethyl-2-imidazolidinethione (12i). Yield 14%; white solid, mp 113–114°C; R_f=0.8 (ethyl acetate/hexane 1:1); ^1H NMR ($CDCl_3$) δ 8.19–8.16 (m, 2H), 7.50–7.35 (m, 8H), 5.22 (s, 2H), 4.15–4.12 (m, 2H), 3.60–3.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 178.2, 177.4, 135.8, 134.2, 132.1, 129.6, 128.9, 128.2, 65.8, 57.5, 47.9; EIMS *m/z* 77.0 (100), 91.5 (77.4), 105.0 (85.2), 191.1 (28.2), 267.1 (21.8), 296.2 (25.9, M). Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.45; H, 5.12; N, 9.69; S, 10.40.

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14. Thioureas **2** under hydrochloric acidic conditions were usually converted into the *S*-cyclized product[9a] and treatment of **2i** with phosphorus hexaethyl triamide produced along with the mixture of *S*-cyclized iminothiazolidine and *N*-cyclized imidazolidinethione in the yield of 36 and 26%, respectively, see: Mizrakh, L. I.; Polonskaya, L. Yu.; Gvozdetskii, A. N.; Berdyugin, V. V.; Vasil'ev, A. M.; Ivanova, T. M. *J. Gen. Chem. USSR (Engl. Transl.)*, **1989**, *59*, 1058–1059; *Zh. Obshch. Khim*, **1989**, *59*, 1195–1196; *Chem. Abstr.*, **1990**, *112*, 55701.
15. All reaction conditions surveyed in Table 1 was applied to **2h**, which gave the mixture of **4h** and **5h** with the following ratios: *t*-BuOK (49/22), NaH (57/38), Et_3N (0/72), and DMAP (0/50). It is noteworthy that the use of triethylamine and DMAP gave the regiospecific *S*-cyclized product without *N*-cyclization.
16. For a regiocontrolled *N*-cyclization reaction of *N*-(2-hydroxyethyl)ureas using TsCl and *t*-BuOK, see: Kim, T. H.; Lee, G.-J. *J. Org. Chem.* **1999**, *64*, 2941–2943.
17. Chiral 2-alkyl or aryl-2-oxazolines have been extensively used in asymmetric synthesis as both ligands and auxiliaries.[18] Aza-bis(oxazolines) as a ligand was attached to a soluble support and successfully applied in asymmetric catalysis, see: Glos, M.; Reiser, O. *Org. Lett.*, **2000**, *2*, 2045–2048. So far chiral **3d** and **3e** were not reported as chiral auxiliaries and we will publish its result in another paper.
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