Ring Closure of *N*-(2-Hydroxyethyl)-*N'*-phenylthioureas: One-Pot Synthesis of 2-Phenylaminothiazolines

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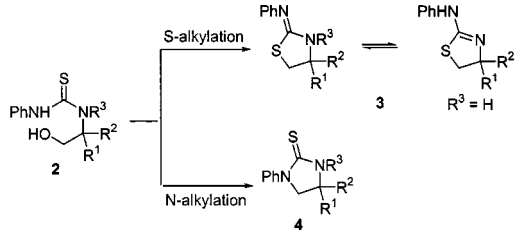
The cyclization reaction of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas **2** containing ambident nucleophile was examined in the combination of a variety of bases and *p*-toluenesulfonyl chloride (TsCl). *N*-(2-Hydroxyethyl)thioureas **2** were readily obtained in high yields from the reaction of the corresponding 1,2-aminoalcohols with phenyl isothiocyanate, avoiding the need for O-protection. The use of a one-pot reaction (NaOH/TsCl) was found to be most effective in producing the requisite 2-phenylaminothiazolines (S-cyclization) **3** in the case of thioureas **2a-2e** derived from *N*-unsubstituted aminoalcohols, while in the thioureas **2f** and **2g** prepared from *N*-substituted aminoalcohols the combination of Et_3N and TsCl led to the S-cyclization products.

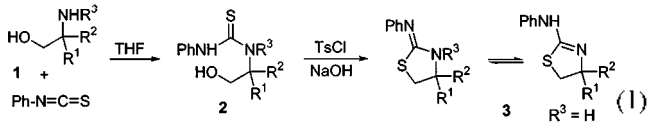
Introduction

The 2-aminothiazoline ring system has gained much interest as biologically active molecules such as potent inhibitors of human nitric oxide synthase,[1] octopaminergic-agonists,[2] anthelmintics,[3] and anti-inflammatory agents.[4] These compounds are usually prepared by the hydrochloric acid-catalyzed cyclization of *N*-(2-hydroxyethyl) thioureas[2a,2b,3,5] or the cyclization of hydrogen sulfate of thioureas[2a,6] in aqueous basic conditions. These methods give low yields for the formation of 2-aminothiazolines and are not applicable to acid sensitive or racemization-prone substrates due to the vigorous acidic reaction conditions. Alternatively, treatment of aromatic amines with 2-haloalkyl isothiocyanates gives 2-aminothiazolines.[7] This method, however, has some limitations in the scope of aromatic amines.[7b]

Recently, we reported that 2-methylaminothiazolines were synthesized selectively from *N*-(2-hydroxyethyl)-*N'*-methylthioureas by the intramolecular Mitsunobu reaction conditions (DEAD/TPP).[8a] To obtain the requisite 2-phenylaminothiazolines, we applied this Mitsunobu reaction conditions to the substrates such as *N*-(2-hydroxyethyl)-*N'*-phenylthioureas **2**. However, with thioureas **2a-2e**, only small amount of 2-phenylaminothiazolines **3** were produced along with unknown mixtures of products. With thioureas **2f-2h**, 2-imidazolidinethiones **4** were mainly obtained.[9] In addition, in the course of our work in the cyclization reaction of *N*-(2-hydroxyethyl)-*N'*-phenylureas, we found that one-pot reaction of *N*-(2-hydroxyethyl)ureas proceeded in the presence of TsCl and some bases to give N-cyclized products in good yields.[8b] On the basis of this reaction conditions, we preliminarily described a successful access to 2-phenylaminothiazolines **3** from the corresponding *N*-(2-hydroxyethyl)-*N'*-phenylthioureas as a more convergent approach. Thioureas **2** proceeded through mild nucleophilic attack upon the tosylate intermediate in the presence of a base either by the sulfur atom to provide **3** or by the nitrogen to give the 2-imidazolidinethiones **4** depending on the structure of thioureas (Scheme 1). In this article the synthetic method of 2-phenylaminothiazolines **3** from the corresponding *N*-(2-hydroxyethyl) thioureas **2** is described in detail (eq. 1).



Scheme 1



Results and Discussion

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 (Table 2). Surveys of one-pot reactions 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 to **2a** in THF (Table 1). In the present reaction, the use of NaOH was found to be most effective in producing 2-phenylaminothiazoline **3a**. The NaOH was added to a mixture of the TsCl and **2a** at room temperature. The reactions were complete within 30 min at room temperature.

The one-pot reaction of various substrates **2a-2h** was examined and the results are shown in Table 2. With thioureas **2a-2e** prepared from N-unsubstituted aminoalcohols (R^3 = H), S-cyclization to **3** was mainly observed with a trace amount of the N-cyclized products. As we expected all reactions proceeded in good yields with regiocontrol (S-cyclization > N-cylization) to give 2-phenylaminothiazolines. However, the thioureas **2f** and **2g** prepared from N-

Table 1. Effect of Base in One-pot Reaction of **2a**

Entry	Base	Time, Temp.	Yield (%)[a] of **3a**
1	*t*-BuOK (2.5 equiv)	30 min, 0 °C	78
2	NaOH (2.5 equiv)	30 min, rt	94
3	NaH (2.5 equiv)	30 min, rt	62
4	Et_3N (5.0 equiv)	17 hr, reflux	62
5	Et_3N/DMAP	17 hr, reflux	33

[a]Isolated yields by column chromatography.

Table 2. Preparations and Cyclizations of *N*-(2-Hydroxyethyl)-thioureas 2

Entry	R^1	R^2	R^3	Yield (%)[a] of **2**	Yield (%)[b] of **3**
a	Me	Me	H	71	94
b	Me	H	H	98	77
c	Et	H	H	99	78
d	(S)-PhCH$_2$	H	H	86	70
e	(S)-*i*-Pr	H	H	85[b]	79
f	H	H	Me	93	29 (40)[c]
g	H	H	Et	91	27 (72)[c]
h	H	H	H	95	[d]

[a]Recrystallized yields. [b]Isolated yields by column chromatography. [c]The yield from the use of Et_3N is in parenthesis. [d]The chlorinated thiourea was mainly obtained in 64% yield.

substituted aminoalcohols (R^3 = Me, Et) gave a mixture of 2-iminothiazolidines (S-alkylation products) and 2-imidazolidinethiones (N-alkylation products) in the ratio of 29/54 and 27/65, respectively. Thiourea **2h** prepared from 2-aminoethanol gave mainly a chlorinated thiourea in a 64% yield, containing a small amount of tosylate (6% yield). To improve the yields of S-cyclized products in the case of **2f** and **2g**, various bases employed above were also applied to **2g** in THF. Contrary to above result, the refluxed reaction in the presence of 5 equiv of Et_3N gave the most effectively S-cyclized product with almost complete regioselectivity. With thiourea **2f** using Et_3N also afforded S-cyclized product in a 40% improved yield. Thus, the use of Et_3N was the most effective to the thioureas **2f** and **2g** derived from N-substituted aminoalcohols. Although a further investigation such as the relationships of the pKa values of thioureas and regioselectivity is needed to understand this reaction, the S-cyclization selectivity is remarkably affected by the base employed depending on the nucleophilicity of thioureas.

In conclusion, we developed a mild synthetic method for 2-phenylaminothiazolines from the corresponding 1,2-aminoalcohols and phenyl isocyanate using one-pot reaction with NaOH/TsCl or Et_3N/TsCl depending on the structure of 1,2-aminoalcohols.

Experimental Section

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

General procedure for the preparation of thiourea 2. To a stirred solution of 1,2-aminoalcohol (4.59 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of phenyl isothiocyanate (0.50 mL, 4.18 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated. The crude products except **2e** were recrystallized to give the requisite product.

***N*-(1,1-Dimethyl-2-hydroxy)ethyl-*N'*-phenylthiourea (2a)**. mp 127-128 °C (toluene); IR ($CDCl_3$, cm^{-1}) 3262, 1278; ^{1}H NMR ($CDCl_3$) δ 7.23-7.43 (5H, m), 6.16 (1H, bs), 3.79 (2H, s), 1.40 (6H, s).

***N*-(2-Hydroxy-1-methyl)ethyl-*N'*-phenylthiourea (2b)**. mp 83-84 °C (hexane/acetone); IR (KBr, cm^{-1}) 3346, 1242; ^{1}H NMR (DMSO) δ 9.50 (1H, s), 7.51 (1H, d, J = 7.9 Hz), 7.04-7.46 (5H, m), 4.87 (1H, t, J = 5.1 Hz), 4.30 (1H, bs), 3.47 (1H, dd, J = 4.8, 10.6 Hz), 3.40 (1H, dd, J = 5.2, 10.6 Hz), 1.10 (3H, d, J = 6.7 Hz); ^{13}C NMR (DMSO) δ 179.9, 139.7, 128.7, 124.1, 123.0, 64.0, 51.2, 17.0.

***N*-(1-Ethyl-2-hydroxy)ethyl-*N'*-phenylthiourea (2c)**. mp 145-146 °C (toluene); IR ($CDCl_3$, cm^{-1}) 3243, 1248; ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, bs), 7.23-7.50 (5H, m), 6.20 (1H, d, J = 7.8 Hz), 4.50 (1H, bs), 3.65-3.91 (2H, m), 2.36 (1H, bs), 1.58 (2H, dq, J = 7.5, 14.0 Hz), 0.96 (3H, t, J = 7.5 Hz).

***N*-[(1S)-2-Hydroxy-1-phenylmethyl]ethyl-*N'*-phenylthiourea (2d)**. mp 103-104 °C (hexane/acetone); IR ($CDCl_3$, cm^{-1}) 3366, 1248; ^{1}H NMR ($CDCl_3$) δ 7.61 (1H, bs), 6.90-7.40 (10H, m), 6.20 (1H, d, J = 7.9 Hz), 4.85 (1H, bs), 3.80 (1H, dd, J = 4.0, 10.9 Hz), 3.63 (1H, dd, J = 4.8, 10.9 Hz), 2.86-2.99 (2H, m), 2.16 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 180.3, 137.1, 135.7, 130.2, 129.2, 128.7, 127.4, 126.8, 125.1, 63.7, 57.4, 36.6.

***N*-[(1S)-2-Hydroxy-1-(1-methylethyl)]ethyl-*N'*-phenylthiourea (2e)**. The crude product was purified by flash column chromatography. R_f = 0.5 (ethyl acetate/hexane 1 : 1); mp 93-95 °C; IR ($CDCl_3$, cm^{-1}) 3273, 1313; ^{1}H NMR ($CDCl_3$) δ 8.83 (1H, bs), 7.19-7.38 (5H, m), 6.45 (1H, d, J = 5.8 Hz), 4.38 (1H, bs), 3.74 (1H, dd, J = 3.8, 11.2 Hz), 3.62 (1H, dd, J = 5.8, 11.2 Hz), 3.39 (1H, bs), 2.98 (1H, bs), 1.80-1.93 (1H, m), 0.90 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 181.0, 136.2, 129.4, 127.5, 125.2, 63.7, 62.1, 29.4, 19.5, 18.9.

***N*-(2-Hydroxyethyl)-*N*-methyl-*N'*-phenylthiourea (2f)**. mp 134-135 °C (hexane); IR ($CDCl_3$, cm^{-1}) 3256, 1346; ^{1}H NMR ($CDCl_3$) δ 7.26-7.38 (5H, m), 3.79-3.87 (4H, m), 3.36(3H, s).

***N*-Ethyl-*N*-(2-hydroxyethyl)-*N'*-phenylthiourea (2g)**. mp 158-159 °C (chloroform/acetone); IR (KBr, cm^{-1}) 3258, 1352; ^{1}H NMR (DMSO) δ 9.43 (1H, bs), 7.05-7.31 (5H, m), 5.53 (1H, bs), 3.79 (2H, q, J = 7.0 Hz), 3.71 (4H, bs), 1.17 (3H, t, J = 7.0 Hz); ^{13}C NMR (DMSO) δ 181.2, 141.1, 128.2, 125.1, 124.3, 60.1, 52.5, 46.5, 12.3.

***N*-(2-Hydroxyethyl)-*N'*-phenylthiourea (2h)**. mp 138-139 °C (chloroform/acetone); IR ($CDCl_3$, cm^{-1}) 3362, 1250; ^1H NMR ($CDCl_3$) δ 7.72 (1H, bs), 7.19-7.48 (5H, m), 6.47 (1H, bs), 3.77-3.85 (4H, m), 1.99 (1H, bs).

General procedure for the preparation of 2-phenylaminothiazolines 3. To a stirred solution thiourea **2** (0.88 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of NaOH (88 mg, 2.2 mmol) in water (3 mL) and TsCl (0.18 g, 0.97 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min, added 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 **3**.

4,5-Dihydro-4,4-dimethyl-*N*-phenyl-2-thiazolamine (3a). mp 114-116 °C; R_f = 0.3 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1687; ^1H NMR ($CDCl_3$) δ 6.93-7.25 (5H, m), 4.02 (2H, s), 1.33 (6H, s); ^{13}C NMR ($CDCl_3$) δ 156.0, aromatics omitted, 78.7, 61.1, 28.0; HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0878, found 206.0864.

4,5-Dihydro-4-methyl-*N*-phenyl-2-thiazolamine (3b). mp 104-105 °C; R_f = 0.3 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1687; ^1H NMR ($CDCl_3$) δ 6.95-7.28 (5H, 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, aromatics omitted, 73.6, 55.3, 21.2; HRMS (EI) calcd for $C_{10}H_{12}N_2S$ 192.0721, found 192.0733.

4,5-Dihydro-4-ethyl-*N*-phenyl-2-thiazolamine (3c). mp 97-98 °C; R_f = 0.2 (ethyl acetate); IR ($CDCl_3$, cm^{-1}) 1703; ^1H NMR ($CDCl_3$) δ 6.94-7.27 (5H, 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, aromatics omitted, 71.9, 60.8, 28.5, 9.7; HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0878, found 206.0876.

(4S)-4,5-Dihydro-*N*-phenyl-4-phenylmethyl-2-thiazolamine (3d). R_f = 0.3 (ethyl acetate/hexane 1 : 1); IR ($CDCl_3$, cm^{-1}) 1687; ^1H NMR ($CDCl_3$) δ 6.95-7.33 (10H, 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, 138.5, 130.1, 129.7, 129.5, 127.5, 123.2, 120.9, 72.4, 63.0, 42.9; HRMS (EI) calcd for $C_{16}H_{16}N_2S$ 268.1034, found 268.1018.

(4S)-4,5-Dihydro-4-(1-methylethyl)-*N*-phenyl-2-thiazolamine (3e). mp 65-67 °C; R_f = 0.3 (ethyl acetate/hexane 1 : 1); IR ($CDCl_3$, cm^{-1}) 1680; ^1H NMR ($CDCl_3$) δ 6.89-7.24 (5H, 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 156.7, 143.3, 128.8, 122.2, 120.8, 70.3, 65.7, 33.0, 18.6, 17.9; HRMS (EI) calcd for $C_{12}H_{16}N_2S$ 220.1034, found 220.1035.

3-Methyl-2-phenyliminothiazolidine (3f). mp 88-89 °C; R_f = 0.5 (ethyl acetate/hexane 3 : 7); IR ($CDCl_3$, cm^{-1}) 1616; ^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, aromatics omitted, 53.0, 33.8, 26.8; EIMS 192 (M, 32), 167 (46), 149 (100), 71 (25), 57 (55); HRMS (EI) calcd for $C_{10}H_{12}N_2S$ 192.0721, found 192.0768.

1-Methyl-3-phenyl-2-imidazolidinethione (4f). mp 88-89 °C; R_f = 0.4 (ethyl acetate/hexane 3 : 7); IR ($CDCl_3$, cm^{-1}) 1336; ^1H NMR ($CDCl_3$) δ 7.21-7.54 (5H, m), 4.01 (2H, m), 3.73 (2H, m), 3.24 (3H, s); ^{13}C NMR ($CDCl_3$) δ 182.0, aromatics omitted, 48.7, 48.5, 35.2; EIMS 192 (M, 11), 91 (38), 77 (100), 57 (60), 51 (54); HRMS (EI) calcd for $C_{10}H_{12}N_2S$ 192.0721, found 192.0749.

3-Ethyl-2-phenyliminothiazolidine (3g). R_f = 0.5 (ethyl acetate/hexane 3 : 7); IR ($CDCl_3$, cm^{-1}) 1624; ^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, aromatics omitted, 50.2, 41.1, 26.7, 11.9; EIMS 206 (M, 1), 77 (100), 56 (57), 51 (45); HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0878, found 206.0840.

1-Ethyl-3-phenyl-2-imidazolidinethione (4g). mp 65-67 °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, aromatics omitted, 48.8, 45.5, 42.4, 11.8; EIMS 206 (M, 91), 106 (97), 77 (100), 51 (45); HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0878, found 206.0864.

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9. Thioureas **2f**, **2g**, and **2h** furnished a mixture of 2-iminothiazolidines and 2-imidazolidinethiones in the ratio of 20/80, 12/88, and 31/69, respectively. The separation and purification of products was not convenient due to the by-products, triphenylphosphine oxide and 1,2-dicarbethoxyhydrazine.