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단 신

TsCl와 염기존재에서의 *N*-(2-Hydroxyethyl)-*N'*-methylthioureas의 고리화반응

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Cyclization Reaction of *N*-(2-Hydroxyethyl)-*N'*-methylthioureas in the Presence of TsCl and Base

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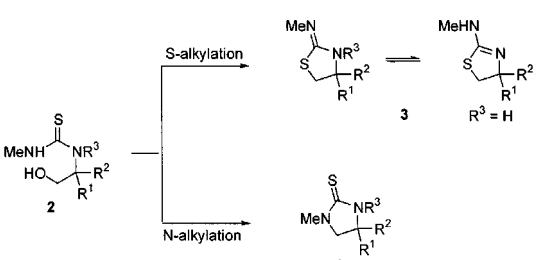
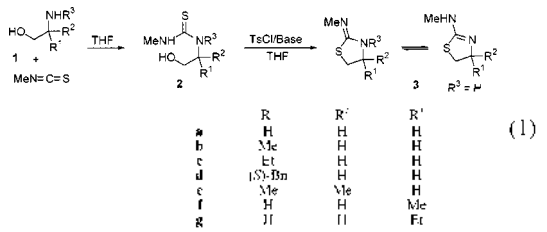
2-Aminothiazolines have gained much interest as biologically active molecules such as potent inhibitors of human nitric oxide synthase,[1] octopaminergic-agonists,[2] anthelmintics,[3] and anti-inflammatory agents.[4] These compounds are usually prepared by the hydrochloric acid-catalyzed cyclization of *N*-(2-hydroxyethyl)thioureas[2a,2b,3,5] or the cyclization of hydrogen sulfate of thioureas in aqueous basic conditions.[2a, 6] These methods give low yields for the formation of the 2-aminothiazolines and are not applicable to acid sensitive or racemization-prone substrates due to the vigorous acidic or basic reaction conditions.

Recently, we preliminarily reported that 2-methylaminothiazolines **3** were synthesized from *N*-(2-hydroxyethyl)-*N'*-methylthioureas **2** by the intramolecular Mitsunobu reaction conditions.[7] The Mitsunobu reaction of **2** proceeded through mild nucleophilic attack upon the oxyphosphonium intermediate either by the sulfur atom to provide 2-aminothiazoline **3** or by the nitrogen to give the 2-imidazolidinethione **4** depending on the structure of **2** (*Scheme* 1). 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. However, the thioureas **2f** and **2g** prepared from N-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 69/31 and 57/43, respectively. Therefore, we needed to develop a new way to 2-methylaminothiazolines to improve more selective yields of S-cyclized products in the case of **2f** and **2g**. In the course of our work in the cyclization reaction of *N*-(2-hydroxyethyl)-*N*-phenylthioureas, we found that one-pot reaction of thioureas proceeds in the presence of TsCl and NaOH to give 2-phenylaminothiazolines in good yields.[8] These results prompted us to examine the one-pot reaction of *N*-(2-hydroxyethyl)-*N'*-methylthioureas **2** for the preparation of **3**. Thioureas **2** were readily prepared from the reaction of the corresponding 1,2-aminoalcohols with methyl iso- thiocyanate in tetrahydrofuran (THF) solution at room temperature in good yields, which provided exclusively the desired products under mild conditions, thus avoiding the need for O-protection. A survey of one-pot reactions by the combination of



Scheme 1.

TsCl with various basic metallic (*t*-BuOK, NaOH, and NaH) or non-metallic (Et_3N/DMAP) reagents was performed to **2** in THF (Eq. 1).



	R	R'	R''
a	H	H	H
b	Me	H	H
c	Et	H	H
d	(*S*)-Bn	H	H
e	Me	Me	H
f	H	H	Me
g	H	H	Et

(1)

One-pot reaction conditions using *t*-BuOK and TsCl were first applied to various thioureas **2**.[9] With **2f** and **2g** prepared from N-substituted aminoalcohols, N-cyclization occurred mainly producing **4f** and **4g** in the yields of 70% and 45%, respectively while with **2a-2e** prepared from N-unsubstituted aminoalcohols, a small amount of 2-methylaminothiazolines **3** were produced along with unknown mixture of products. Contrary to *N*-(2-hydroxyethyl)-*N'*-phenylthioureas, the application of the reaction conditions using NaOH/TsCl also gave unacceptable results regardless of the structure of thioureas **2**. To improve the nucleophilicity of thioureas **3** the combination of more basic NaH and TsCl was explored to various thioureas **2** which resulted in unknown mixture or low selectivity and conversion yields. However, **2g** under NaH/TsCl gave only the N-cyclization product with a 75% conversion. The above reaction conditions in the case of **2f** and **2g** gave unsatisfactory results to prepare the 2-methylaminothiazolines, leading to N-cyclization to **4f** and **4g**.

We next turned to use a non-metallic basic reagent, Et_3N/DMAP. The refluxed reaction in the presence of 5 equiv of Et_3N and 0.5 equiv of DMAP gave S-cyclized and N-cyclized mixtures in the case of **2a-2e**. With thiourea **2f** and **2g**, however, the essential 2-methylaminothiazolines were obtained in 85% and 90% yields, respectively. Thus, the use of Et_3N/DMAP in the case of **2f** and **2g** was the most effectively S-cyclized product with almost complete regioselectivity. Although further investigation is needed to understand these reactions, the S-cyclization selectivity is remarkably affected by the base employed depending on the nucleophilicity of thioureas.

Mitsunobu reaction was a condition for the regiocontrolled conversion of the only thioureas **2a-2e** derived from N-unsubstituted aminoalcohols into 2-methylaminothiazolines.[7] Most of one-pot reaction conditions of thioureas **2** using the combination of bases and TsCl produced the mixture of S- or N-cyclized products depending on the substrates and bases. However, the use of Et_3N/DMAP was the most effective condition for the regiospecific conversion of the thioureas **2f** and **2g** derived from N-substituted aminoalcohols into the requisite S-cyclized products.

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 $CDCl_3$ as solvent and 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 methyl 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, and purified by flash column chromatography to give **2**.

***N*-(2-Hydroxyethyl)-*N'*-methylthiourea (2a).** Yield: 92%; mp 70-72 °C; R_f = 0.2-0.3 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.82 (2H, dd, *J*=4.2, 1.2), 3.69 (2H, bs), 3.02 (3H, d, *J*=4.5).

***N*-[(2-Hydroxy-1-methyl)ethyl]-*N'*-methylthiourea (2b).** Yield: 66%; R_f =0.4 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (2H, dd, *J*=3.5, 11.1), 3.55 (1H, dd, *J*=6.9, 11.0), 3.01(3H, d, *J*=4.4), 1.21 (3H, d, *J*=6.7).

***N*-[(1-Ethyl-2-hydroxy)ethyl]-*N'*-methylthiourea (2c).** Yield: 81%; R_f =0.5 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (1H, dd, *J*=3.4, 11.1), 3.59 (2H, dd, *J*=6.8, 11.1), 3.02 (2H, d, *J*=4.5), 1.49-1.65 (2H, m), 0.98 (3H, t, *J*=7.4).

***N*-[[(1S)-2-Hydroxy-1-phenylmethyl]ethyl]-*N'*-methylthiourea (2d).** Yield: 85%; R_f=0.3-0.5 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.31 (5H, m), 3.75 (1H,

dd, J=3.6, 11.1), 3.59 (1H, dd, J=5.7, 11.1), 2.82-3.01 (2H+1H, m), 2.90 (3H, d, J=3.3).

***N*-[(1,1-Dimethyl-2-hydroxy)ethyl]-*N'*-methylthiourea (2e).** Yield: 80%; R_f=0.5 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (2H, s), 3.06 (3H, d, J=4.5), 1.32 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) d 181.4, 70.4, 57.0, 32.1, 24.5.

***N*-(2-Hydroxyethyl)-*N*-methyl-*N'*-methylthiourea (2f).** Yield: 75%; R_f=0.3 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (4H, s), 3.23 (3H, s), 3.12 (3H, d, J=4.5).

***N*-Ethyl-*N*-(2-hydroxyethyl)-*N'*-methylthiourea (2g).** Yield: 95%; R_f=0.4 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.88 (2H, m), 3.80-3.71 (4H, m), 3.09 (3H, d, J=4.5), 1.24 (3H, t, J=7.2).

General procedure for the preparation of 2-methylaminothiazolines 3

TsCl/Metallic Base Conditions: To a stirred solution thiourea **2** (0.88 mmol) and base (2.2 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of 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** or **4**.

TsCl/Et$_3$N/DMAP Conditions: To a stirred solution thiourea **2** (0.88 mmol) and triethylamine (0.61 mL, 4.4 mmol) and 4-(dimethylamino)pyridine (49 mg, 0.44 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of TsCl (0.18 g, 0.97 mmol) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was refluxed over night, 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** or **4**.

4,5-Dihydro-*N*-methyl-2-thiazolamine (3a). mp 90 °C; R_f=0.1-0.3 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00(2H, t, J=7.4), 3.34(2H, t, J=7.4), 2.93(3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) d 162.9, 59.8, 35.3, 31.3; HRMS (EI) calcd for $C_4H_8N_2S$ 116.0408 found 116.0428.

4,5-Dihydro-4-methyl-*N*-methyl-2-thiazolamine (3b). mp 72-75 °C; R_f=0.1-0.2 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37-4.44 (1H, m), 3.56 (1H, dd, J=3.6, 10.8), 3.10 (1H, dd, J=3.9, 10.8), 3.02 (3H, s), 1.45 (3H, d, J=5.1); ^{13}C NMR (75 MHz, $CDCl_3$) d 161.3, 67.3, 41.2, 31.3, 21.3; HRMS (EI) calcd for $C_5H_{10}N_2S$ 130.0564, found 130.0545.

4,5-Dihydro-4-ethyl-*N*-methyl-2-thiazolamine (3c). mp 61 °C; R_f=0.1-0.2 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09-4.22 (1H, m), 3.40 (1H, dd, J=7.2, 10.5), 3.00 (1H, dd, J=7.3, 10.5), 2.93 (3H, s), 1.71-1.85 (1H, m), 1.49-1.64 (1H, m), 0.99 (3H, t, J=7.4); ^{13}C NMR (75 MHz, $CDCl_3$) d 161.0, 73.9, 39.1, 31.5, 28.7, 10.9; HRMS (EI) calcd for $C_6H_{12}N_2S$ 144.0721, found 140.0709.

(4S)-4,5-Dihydro-*N*-methyl-4-phenylmethyl-2-thiazolamine (3d). mp 105 °C; R_f=0.1-0.2 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.33 (5H, m), 4.42-4.51 (1H, m), 3.23 (1H, dd, J=7.2, 10.8), 3.15 (1H, dd, J=4.8, 13.5), 3.06 (1H, dd, J=5.7, 10.8), 2.17 (1H, dd, J=9.3, 13.5), 2.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 138.9, 129.1, 128.3, 126.1, 73.3, 41.3, 38.4, 31.4; HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0877, found 206.0838.

4,5-Dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine (3e). mp 110 °C; R_f=0.1-0.2 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (2H, s), 2.94 (3H, s), 1.42 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 73.1, 46.2, 31.4, 28.3; HRMS (EI) calcd for $C_6H_{12}N_2S$ 144.0721, found 144.0737.

3-Methyl-2-methyliminothiazolidine (3f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (2H, t, J=6.6), 3.12 (2H, t, J=6.6), 3.04 (3H, s), 2.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 53.2, 41.5, 33.8, 26.8.

1,3-Dimethyl-2-imidazolidinethione (4f). R_f=0.7 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (4H, s), 3.13 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 183.4, 48.2, 35.0.

3-Ethyl-2-methyliminothiazolidine (3g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (2H, t, J=6.6), 3.37 (2H, q, J=7.2), 3.13 (2H, t, J=6.6), 3.04 (3H, s), 1.14 (3H, t, J=7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 50.2, 41.4, 41.0, 26.7, 12.0.

1-Ethyl-3-methyl-2-imidazolidinethione (4g). R_f=0.7 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (2H, q, J=7.2), 3.54 (4H, s), 3.13 (3H, s), 1.17 (3H, t, J=7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6, 48.3, 45.3, 42.4, 34.8, 12.0.

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