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

Namgun Lee, Mi-Hyun Cha, and Taek Hyeon Kim*
Faculty of Applied Chemistry, Chonnam National University, Kwangju 500-757, Korea
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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 antiepileptics,3 and anti-inflammatory agents.4 These compounds are usually prepared by the hydrochloric acid-catalyzed cyclization of N-(2-hydroxyethyl)thioureas202434 or the cyclization of hydrogen sulfide of thioureas in aqueous basic conditions.2526 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 a nucleophilic attack upon the oxaphosphonium intermediate either by the sulfur atom to provide 2-aminothiazolines 3 or by the nitrogen to give the 2-imidazolidinediones 4 depending on the structure of 2 (Scheme 1). With thioureas 2a-2e prepared from N-unsubstituted aminoalcohols (R2-H), S-alkylation to 3 was mainly observed with a trace amount of the N-alkylated products. However, the thioureas 2f and 2g prepared from N-substituted aminoalcohols (R2-Me, Et) gave a mixture of 2-iminothiazolines (S-alkylation products) and 2-imidazolidinediones (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-alkylated 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.5 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 isothiocyanate 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](image-url)
TsCl with various basic metallic (Li, NaOH, NaNH, and NaI) or non-metallic (HN/DMAP) reagents was performed to 2 in THF (Eq. 1).

One-pot reaction conditions using -BuOK and TsCl were first applied to various thioureas 2. With 2f and 2g prepared from N-substituted aminalcohols, N-acylation occurred mainly producing 4f and 4g in the yields of 70% and 45%, respectively, while with 2a-2e prepared from N-unsubstituted aminalcohols, a small amount of 2-methylaminothiazolines 3 were produced along with unknown mixture of products. Contrary to N-(2-hydroxy-ethyl)-N'phenylthiourea, the application of the reaction conditions using NaOH/TsCl also gave unacceptable results regardless of the structure of thiourea 2. To improve the nucleophilicity of thioureas 3 the combination of more basic NaI and TsCl was explored to various thioureas 2 which resulted in unknown mixture or low selectivity and conversion yields. However, 2g under NaI/TsCl gave only the N-acylation product with a 75% conversion. The reaction conditions in the case of 2f and 2g gave unsatisfactory results to prepare 4f and 4g.

We next turned to use a non-metallic basic reagent, Et$_2$N/DMAP. The refluxed reaction in the presence of 5 equiv of Et$_2$N and 0.5 equiv of DMAP gave S-acylated and N-acylated mixtures in the case of 2a-2e. With thioure 2f and 2g, however, the essential 2-methylaminothiazolines were obtained in 85% and 90% yields, respectively. Thus, the use of Et$_2$N/DMAP in the case of 2f and 2g was the most effectively S-acylated product with almost complete regioselectivity. Although further investigation is needed to understand these reactions, the S-acylation selectivity is remarkably affected by the base employed depending on the nucleophilicity of thioureas.

Mitsunobu reaction was a condition for the regio-controlled conversion of the only thioureas 2a-2e derived from N-unsubstituted aminoalcohols into 2-methylaminothiazolines. Most of one-pot reaction conditions of thiourea 2 using the combination of bases and TsCl produced the mixture of S- or N-acylated products depending on the substrates and bases. However, the use of Et$_2$N/DMAP was the best effective condition for the regiospecific conversion of the thioureas 2f and 2g derived from N-substituted aminoalcohols into the requisite S-acylated products.

**Experimental Section**

General. $^1$H NMR and $^{13}$C NMR spectra were recorded using 300 MHz and 75 MHz NMR spectrometers; chemical shifts are reported in ppm using CDCl$_3$ as a solvent and TMS as an internal standard. Melt point was determined on a capillary apparatus and uncorrected. Mass spectra were recorded on a HP 5883B 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-aminolcohol (4.59 mmol) in THF (10 mL) under nitrogen at room temperature was added a solution of methyl isothiocyanate (0.50 mol, 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-methylthiethyl]-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 (2H, dd, J=6.9, 11.0), 3.01 (3H, d, J=4.1), 1.21 (3H, d, J=6.7).

N-[1-Ethyl-2-hydroxyethyl]-N'-methylthiourea (2c). Yield: 81%; R$_f$: 0.5 (ethyl acetate); $^1$H NMR (300 MHz, CDCl$_3$) δ 3.78 (2H, dd, J=3.4, 11.1), 3.59 (2H, dd, J=6.8, 11.1), 3.02 (2H, d, J=4.5), 1.49-1.63 (2H, m), 0.98 (3H, t, J=7.4).

N-[1(1S)-2-Hydroxy-1-phenylmethyl]thiethyl]-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 (111, dd, J = 5.7, 11.1); 2.83-3.01 (2H, 111, m), 2.90 (111, d, J = 3.3).

N-{[1,1-Dimethyl-2-hydroxyethyl]-N'-methylthiourea (26). Yield: 80%. R = 0.5 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.65 (2H, s), 3.05 (3H, d, J = 4.5), 1.32 (6H, s), 13C NMR (75 MHz, CDCl3) δ 181.4, 70.4, 57.0, 32.1, 24.5.

N-(2-Hydroxyethyl)-N'-methylthiourea (27). Yield: 75%. R = 0.3 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.88 (4H, s), 3.23 (3H, s), 3.12 (3H, d, J = 4.5).

N-Acetyl-N-{2-(hydroxyethyl)-N'-methylthiourea (28). Yield: 95%. R = 0.4 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.85-3.88 (2H, m), 3.80-3.71 (4H, m), 3.05 (3H, d, J = 4.5), 1.24 (3H, t, J = 7.2).

General procedure for the preparation of 2-methylthioanilinothiazolines 3

TsCl/Metallic Base Conditions: To a stirred solution of 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). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give 3 or 4.

TsCl/0.5N/DMAP Conditions: To a stirred solution of 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). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give 3 or 4.

4.5-Dihydro-4-ethyl-N'-methyl-2-thiazoline (30). mp 90°C; R = 0.1-0.3 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 4.00 (2H, t, J = 7.4), 3.34 (2H, t, J = 7.4), 2.95 (3H, s); 13C NMR (75 MHz, CDCl3) δ 162.9, 59.8, 35.3, 31.3, 113.1, HRMS (EI) for C8H15N5S. 1H NMR (300 MHz, CDCl3) 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 = 3.1). 31C NMR (75 MHz, CDCl3) δ 161.3, 67.3, 41.2.

dd, J = 3.6, 11.1); 3.59 (111, dd, J = 5.7, 11.1); 2.83-3.01 (2H, 111, m), 2.90 (111, d, J = 3.3).

4.5-Dihydro-4-ethyl-N'-methyl-2-thiazoline (30). mp 90°C; R = 0.1-0.3 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 4.00 (2H, t, J = 7.4), 3.34 (2H, t, J = 7.4), 2.95 (3H, s); 13C NMR (75 MHz, CDCl3) δ 162.9, 59.8, 35.3, 31.3, 113.1, HRMS (EI) for C8H15N5S. 1H NMR (300 MHz, CDCl3) 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 = 3.1). 31C NMR (75 MHz, CDCl3) δ 161.3, 67.3, 41.2.

13-Dimethyl-2-imidazolidinethione (40). R = 0.7 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.54-4.6 (4H, s), 3.13 (6H, s); 13C NMR (75 MHz, CDCl3) δ 183.4, 48.2, 35.0.

3-Ethyl-2-methylthioanilinothiazoline (3g). 1H NMR (300 MHz, CDCl3) δ 3.46 (2H, t, J = 6.6), 3.37 (2H, t, J = 7.2), 3.13 (2H, t, J = 6.6), 3.04 (3H, s), 1.14 (3H, t, J = 7.2); 13C NMR (75 MHz, CDCl3) δ 156.7, 50.2, 41.4, 41.0, 26.7, 12.0.

1-Ethyl-3-methyl-2-imidazolidinethione (4g). R = 0.7 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.67 (2H, q, J = 7.2), 3.54 (4H, s), 3.13 (3H, s), 1.17 (3H, t, J = 7.2); 13C NMR (75 MHz, CDCl3) δ 182.6, 48.3, 45.3, 42.4, 34.8, 12.0.

REFERENCES

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TsCl과 염기존재에서의 N-(2-Hydroxyethyl)-N-methylthioureas의 고리화반응


