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
(Received November 28, 2000)

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)thioureas2a,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-methylaminothiazolines3 were synthesized from N-(2-hydroxyethyl)-N'-methylthioureas2 by the intramolecular Mitsunobu reaction conditions.7 The Mitsunobu reaction of 2 proceeded through mild nucleophilic attack upon the oxypophonium intermediate either by the sulfur atom to provide 2-aminothiazoline3 or by the nitrogen to give the 2-imidazolidinethione4 depending on the structure of 2 (Scheme 1). With thioureas 2a-2e prepared from N-unsubstituted aminoisothiocyanates (R3=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 aminoisothiocyanates (R3=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 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
Thus, the use of Et$_3$N/DMAP in the case of azolines were obtained in 85% and 90% yields, respectively.

Mitsunobu reaction was a condition for the regiocontrolled conversion of the only thioureas depending on the nucleophilicity of thioureas. More basic NaH and TsCl was explored to various thioureas which resulted in unknown mixture or low selectivity and conversion yields. However, the use of Et$_3$N/DMAP was the most effective condition for the regiospecific conversion of the 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$_3$N/DMAP was the most effective condition for the S-cyclization to product 2. One-pot reaction conditions using $t$-BuOK and TsCl were first applied to various thioureas. With 2f and 2g prepared from N-unsubstituted aminoalcohols into 2-methylaminothiazolines, leading to N-cyclization to product 2.

One-pot reaction conditions using $t$-BuOK and TsCl were first applied to various thioureas. With 2f and 2g prepared from N-unsubstituted aminoalcohols, N-cyclization occurred mainly producing 4f and 4g in the yields of 70% and 45%, respectively, while with 2a-2e prepared from N-substituted aminoalcohols, a small amount of 2-methylaminothiazolines 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. To improve the nucelophilicity 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$_3$N/DMAP. The refluxed reaction in the presence of 5 equiv of Et$_3$N 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$_3$N/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. 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$_3$N/DMAP was the most effective condition for the S-cyclization to product 2.

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, $J_{2,3}=4.2$), 3.69 (2H, bs), 3.02 (3H, d, $J_{3,4}=4.5$).

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, $J_{3,4}=3.5$), 1.49-1.65 (2H, m), 0.98 (3H, d, $J=6.9$), 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, $J=3.4$), 3.59 (2H, dd, $J=6.8$), 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,
d, 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-hydroxyethyl]-N'-methylthiourea (2e).
Yield: 80%; Rf=0.5 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.65 (2H, s), 3.06 (3H, d, J=4.5), 1.32 (6H, s); 13C NMR (75 MHz, CDCl3) δ 163.4, 70.4, 57.0, 32.1, 24.5.

N-(2-Hydroxyethyl)-N-methyl-N'-methylthiourea (2f).
Yield: 75%; Rf=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-Ethyl-N-(2-hydroxyethyl)-N'-methylthiourea (2g).
Yield: 95%; Rf=0.4 (ethyl acetate); 1H NMR (300 MHz, CDCl3) 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-methylothiazolines 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×3). The organic layer was dried, filtered, and evaporated, and purified by flash column chromatography to give 3 or 4.

TsCl/Et3N/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×3). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give 3 or 4.

4,5-Dihydro-N-methylthiazolamine (3a).
mp 90°C; Rf=0.1-0.2 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.42 (2H, t, J=6.6), 3.12 (2H, t, J=7.2), 3.04 (3H, s), 2.85 (3H, s); 13C NMR (75 MHz, CDCl3) δ 160.8, 53.2, 41.5, 33.8, 26.8.

1,3-Dimethyl-2-imidazolidinethione (4a).
Rf=0.7 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.54 (4H, s), 3.13 (6H, s); 13C NMR (75 MHz, CDCl3) δ 183.4, 48.2, 35.0.

3-Ethyl-2-methylthiazolidinethione (3g).
mp 110°C; Rf=0.1-0.2 (ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 3.71-3.73 (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); 13C NMR (75 MHz, CDCl3) δ 167.7, 138.9, 129.1, 128.3, 73.3, 41.3, 38.4, 31.4, HRMS (EI) calc for C12H14N2S 144.0737.

REFERENCES
1. (a) Southan, G. J.; Zingarelli, B.; O'Connor, M.; Salz-


---

**Citation:**