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Efficient Synthesis of 2-Methylaminothiazolines via Mitsunobu Reaction of *N*-(2-Hydroxyethyl)-*N'*-methyl-thioureas

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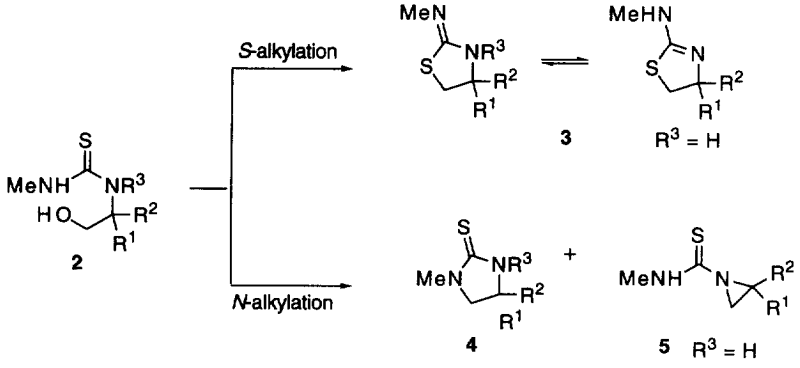
Abstract: 2- Methylaminothiazolines **3** were synthesized selectively from *N*-(2-hydroxyethyl)-thioureas **2** by the intramolecular Mitsunobu reaction.

Keywords: 2-methylaminothiazolines; N-(2-hydroxyethyl)-N'-methyl-thioureas; intramolecular Mitsunobu reaction

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 antiinflammatory 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 the 2-aminothiazolines and are not applicable to acid sensitive or racemization-prone substrates due to the vigorous acidic or basic reaction conditions.



Scheme 1

Mitsunobu reaction of thioureas such as **2** can conceivably proceed through mild nucleophilic attack upon the oxyphosphonium intermediate either by the sulfur atom to provide 2-aminothiazoline **3** or by the two nitrogens to

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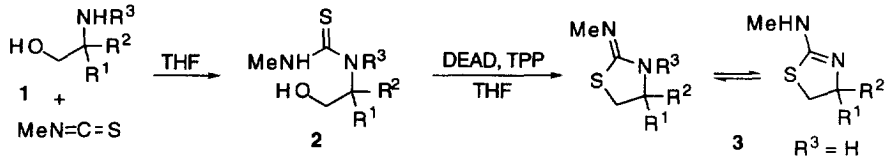
give the 2-imidazolidinethione **4** or aziridine **5** (Scheme 1). However, we speculated that the increased nucleophilicity of sulfur atom relative to nitrogen may favor 2-aminothiazoline formation. Herein we report a mild access to 2-aminothiazolines at room temperature from the corresponding *N*-(2-hydroxyethyl)-thioureas through a selective intramolecular Mitsunobu reaction (eq. 1).

Table 1. Intramolecular Mitsunobu Reaction of *N*-(2-Hydroxyethyl)-thioureas



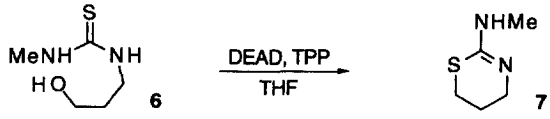
(1)

entry	R^1	R^2	R^3	yield (%) of **2**[a]	yield (%) of **3**	mp (°C) of **3**	yield (%) of **3** HCl	mp (°C) of **3** HCl
a	H	H	H	92	87	90[b]	90	154-157
b	Me	H	H	66	75	72-75	92	140-142
c	Et	H	H	81	73	61	82	126-128
d	(*S*)-Bn	H	H	85	66	105	74	175-178
e	Me	Me	H	80	75	110	82	178-182
f	H	H	Me	75	(69/31)[c]	-	57	140-143
g	H	H	Et	95	(57/43)[c]	-	40	128-130

[a]Isolated yields by column chromatography. [b]Lit.[8] mp 88.5-90 °C. [c]The ratios of a mixture, 2-iminothiazolidine and 2-imidazolidinethione, were determined with NMR data.

N-(2-Hydroxyethyl)-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 (Table 1). The Mitsunobu reaction was achieved with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) in THF.[7] The DEAD was added to a mixture of the TPP and **2** at room temperature. The reactions were complete within 30 min at room temperature. Generally, the separation and purification of the Mitsunobu reaction products are not convenient because the by-products, triphenylphosphine oxide and 1,2-dicarbethoxyhydrazine have similar Rf values to products. However, the 2-aminothiazolines were cleanly isolated after precipitation as HCl salts upon addition of 1-2 equivalent ethanolic HCl to the reaction mixture.

The intramolecular Mitsunobu reaction of various substrates **2a-2g** was examined: The results are shown in Table 1. With thioureas **2a-2e** prepared from *N*-unsubstituted aminoalcohols (R^3=H), *S*-cyclization to 2-aminothiazolines was mainly observed with trace amount of the *N*-cyclized products **4**. Thus, all reactions proceeded in good yields with regiocontrol (*S*-cyclization > *N*-cylization) to give 2-aminothiazolines, as we expected. 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. The desired products were also conveniently isolated as HCl salts. To expand the scope of this methodology,[9] the intramolecular Mitsunobu reaction of *N*-(3-hydroxypropyl)-*N'*-methyl thiourea **6** was performed giving the *S*-alkylation product **7** (HCl salt: 91% yield, mp 149-151 °C; free base: 78% yield, mp 47-51 °C).



In conclusion, we have succeeded in the development of a mild synthetic method for 2-methylaminothiazolines from the corresponding 1,2-aminoalcohols using a selective Mitsunobu reaction. Aminothiazolines were efficiently isolated as the HCl salts in good to excellent yields.

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References and Notes

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[7] Synthesis of 4,5-dihydro-*N*-methyl-2-thiazolamine (**3a**) : To a stirred solution of *N*-(2-hydroxyethyl)-*N'*-methyl-thiourea **2a** (0.2 g, 1.49 mmol) and triphenylphosphine (0.59 g, 2.24 mmol) in THF (20 mL) under nitrogen at room temperature was added a solution of diethyl azodicarboxylate (0.46 mL, 2.24 mmol) in THF (10 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min. 0.1 N HCl in ethanol (0.6 mL, 1.49 mmol) was added dropwise over 15 min. The resulting solution was cooled to 5 °C over night. The product was isolated by filtration and washed with chilled THF (2 x 10 mL). Drying *in vacuo*

for 18 h provided **3a** HCl (0.2 g, 90% yield) as solid. To obtain the free base **3a**, the product was dissolved in THF (20 mL) and 0.1 N NaOH (0.6 mL, 1.49 mmol) and extracted with chloroform (2 x 20 mL). The organic layer was dried, filtered, and evaporated to give **3a** (0.15 g. 87% yield).

4,5-dihydro-*N*-methyl-2-thiazolamine (3a)

^{1}H NMR (300 MHz, $CDCl_3$) 4.00(2H, t, *J*=7.4), 3.34(2H, t, *J*=7.4), 2.93(3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 31.25, 35.19, 59.78, 162.92; HRMS(EI) calcd for $C_4H_8N_2S$ 116.0408 found 116.0428; 3aHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 10.33(2H, bs), 4.01(2H, t, *J*=7.5), 3.52(2H, t, *J*=7.5), 3.08(3H, d, *J*=5.1).

4,5-dihydro-4-methyl-*N*-methyl-2-thiazolamine (3b)

^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 21.26, 31.33, 41.23, 67.31, 161.30; HRMS (EI) calcd for $C_5H_{10}N_2S$ 130.0564, found 130.0545; 3bHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 10.31 (2H, bs), 4.38-4.45 (1H, m), 3.59 (1H, dd, *J*=7.2, 10.8), 3.13 (1H, dd, *J*=7.5, 10.8), 3.05 (3H, d, *J*=4.5), 1.47 (3H, d, *J*=6.6).

4,5-dihydro-4-ethyl-*N*-methyl-2-thiazolamine (3c)

^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 10.85, 28.70, 31.51, 39.09, 73.90, 160.96; HRMS (EI) calcd for $C_6H_{12}N_2S$ 144.0721, found 140.0709; 3cHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 10.48 (1H, bs), 10.19 (1H, bs), 4.16-4.23 (1H, m), 3.57 (1H, dd, *J*=7.2, 11.1), 3.18 (1H, dd, *J*=7.5, 11.1), 3.05 (3H, d, *J*=5.1), 1.69-1.89 (2H, m), 1.08 (3H, t, *J*=7.5).

(4S)-4,5-dihydro-*N*-methyl-4-phenylmethyl-2-thiazolamine (3d)

^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 31.35, 38.44, 41.25, 73.25, 126.10, 128.26, 129.08, 138.90, 161.71; HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0877, found 206.0838; 3dHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 10.55 (1H, bs), 10.37 (1H, bs), 7.20-7.39 (5H, m), 4.45-4.54 (1H, m), 3.41 (1H, dd, *J*=7.5, 11.4), 3.24 (1H, dd, *J*=6.3, 11.4), 3.18 (1H, dd, *J*=4.8, 13.8), 2.93 (1H, dd, *J*=8.7, 13.8), 3.03 (3H, d, *J*=5.1).

4,5-dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine (3e)

^{1}H 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; HRMS (EI) calcd for $C_6H_{12}N_2S$ 144.0721, found 144.0737; 3eHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 10.23 (1H, bs), 10.06 (1H, bs), 3.30 (2H, s), 3.04 (3H, d, *J*=5.1), 1.55 (6H, s).

3-methyl-2-methylimino-thiazolidine (3f)

3fHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 11.52 (1H, bs), 4.07 (2H, t, *J*=7.5), 3.54 (2H, t, *J*=7.5), 3.51 (3H, s), 3.13 (3H, d, *J*=4.5).

3-ethyl-2-methylimino-thiazolidine (3g)

^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 11.95, 26.68, 40.96, 41.40, 50.24, 156.73; 3gHCl: ^{1}H NMR (300 MHz, $CDCl_3$) 11.66 (1H, bs), 3.99-4.06 (4H, m), 3.50 (2H, t, *J*=7.5), 3.13 (3H, t, *J*=7.2)

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[9] The Mitsunobu reaction of the thioureas derived from phenyl isocyanate is possible, but with the aminoalcohol **1a**, **1f**, and **1g**, *N*-alkylation products were mainly obtained. With the amino alcohol **1b**, **1c**, **1d**, and **1e**, only small amount of *S*-alkylation products was produced along with unknown mixtures of products.