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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. © 1999 Elsevier Science Ltd. All rights reserved.

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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.



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

H (1 M	NHF D R H HeN=C=S	₹ ³ } ²	THF	$ \begin{array}{c} S \\ MeNH \\ HQ \\ R^2 \\ R^1 \\ 2 \end{array} $	DEAD, TPI THF		MeHN	$\frac{1}{R^{2}} = H$ (1)
entry	R1	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	Н	Н	Н	92	87	90b	90	154-157
b	Me	н	Н	66	75	72-75	92	140-142
c	Et	н	н	81	73	61	82	126-128
d	(<i>S</i>)-Bn	Н	Н	85	66	105	74	175-178
e	Me	Me	e H	80	75	110	82	178-182
f	Н	н	Me	75	(69/31) ^c	-	57	140-143
g	Н	н	Et	95	(57/43) ^c	-	40	128-130

^aIsolated yields by column chromatography. ^bLit.⁸ mp 88.5-90 °C. ^cThe ratios of a mixture, 2iminothiazolidine and 2-imidazolidinethione, were determined with NMR data.

N-(2-Hydroxyethyl)-thioureas **2** were readily prepared from the reaction of the corresponding 1,2aminoalcohols 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 (R³=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 (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. 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)

¹H NMR (300 MHz, CDCl₃) 4.00(2H, t, J=7.4), 3.34(2H, t, J=7.4), 2.93(3H, s); ¹³C NMR (75 MHz, CDCl₃) 31.25, 35.19, 59.78, 162.92; HRMS(EI) calcd for C₄H₈N₂S 116.0408 found 116.0428; 3aHCl: ¹H NMR (300 MHz, CDCl₃) 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)

¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 21.26, 31.33, 41.23, 67.31, 161.30; HRMS (EI) calcd for C₅H₁₀N₂S 130.0564, found 130.0545; 3bHCl: ¹H NMR (300 MHz, CDCl₃) 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)

¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 10.85, 28.70, 31.51, 39.09, 73.90, 160.96; HRMS (EI) calcd for C₆H₁₂N₂S 144.0721, found 140.0709; 3cHCl: ¹H NMR (300 MHz, CDCl₃) 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)

¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 31.35, 38.44, 41.25, 73.25, 126.10, 128.26, 129.08, 138.90, 161.71; HRMS (EI) calcd for C₁₁H₁₄N₂S 206.0877, found 206.0838; 3dHCl: ¹H NMR (300 MHz, CDCl₃) 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)

¹H NMR (300 MHz, CDCl₃) 3.26 (2H, s), 2.94 (3H, s), 1.42 (6H, s); ¹³C NMR (75 MHz, CDCl₃) 28.28, 31.38, 46.16, 73.11, 159.43; HRMS (EI) calcd for C₆H₁₂N₂S 144.0721, found 144.0737; 3eHCl: ¹H NMR (300 MHz, CDCl₃) 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: ¹H NMR (300 MHz, CDCl₃) 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)

¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 11.95, 26.68, 40.96, 41.40, 50.24, 156.73; 3gHCl: ¹H NMR (300 MHz, CDCl₃) 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.