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One-pot synthesis of 2-phenylaminothiazolines from *N*-(2-hydroxyethyl)-*N'*-phenylthioureas

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Abstract

2-Phenylaminothiazolines **3** were synthesized from *N*-(2-hydroxyethyl)-*N'*-phenylthioureas **2** by a one-pot reaction using *p*-toluenesulfonyl chloride (TsCl) and NaOH or Et_3N.

Keywords: 2-phenylaminothiazolines; *N*-(2-hydroxyethyl)-*N'*-phenylthioureas; one-pot reaction.

The 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 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[2a,6] in aqueous basic conditions. These methods give low yields for the formation of 2-aminothiazolines and are not applicable to acid sensitive or racemization-prone substrates due to the vigorous acidic reaction conditions. Alternatively, treatment of aromatic amines with 2-haloalkyl isothiocyanates gives 2-aminothiazolines.[7] This method, however, has some limitations in the scope of aromatic amines.[7b]

Recently, we reported that 2-methylaminothiazolines are synthesized selectively from *N*-(2-hydroxyethyl)-*N'*-methylthioureas by the intramolecular Mitsunobu reaction.[8a] To obtain 2-phenylaminothiazolines, we applied Mitsunobu reaction conditions to the substrates such as *N*-(2-hydroxyethyl)-*N'*-phenylthioureas **2**. However, with thioureas **2a–2e**, only small amounts of 2-phenylaminothiazolines **3** were produced along with an unknown mixtures of products. With thioureas **2f–2h**, 2-imidazolidinethiones **4** were mainly obtained. In addition, in the course of our work in the cyclization reaction of *N*-(2-hydroxyethyl)-*N'*-phenylureas, we found that one-pot reaction of *N*-(2-hydroxyethyl)ureas proceeds in the presence of TsCl and *t*-BuOK to give *N*-cyclized products in good yields.[8b] These results prompted us to examine the one-pot reaction of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas for the preparation of **3** or **4** as a more convergent approach.

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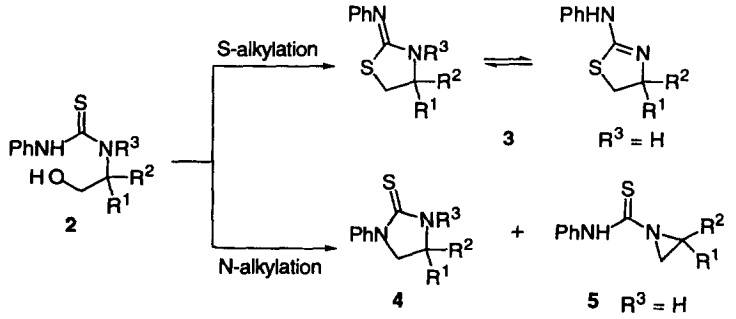
Thioureas **2** can conceivably proceed through mild nucleophilic attack upon the tosylate intermediate in the presence of a base either by the sulfur atom to provide 2-aminothiazoline **3** or by the two nitrogens to give the 2-imidazolidinethione **4** or aziridine **5** (Scheme 1). However, we expected that the increased nucleophilicity of sulfur atom relative to nitrogen may favor 2-aminothiazoline formation. Herein we report a mild access to 2-phenylaminothiazolines **3** at room temperature from the corresponding *N*-(2-hydroxyethyl) thioureas **2** through one-pot reaction with TsCl and some bases (see Eq. 1 in Table 1).

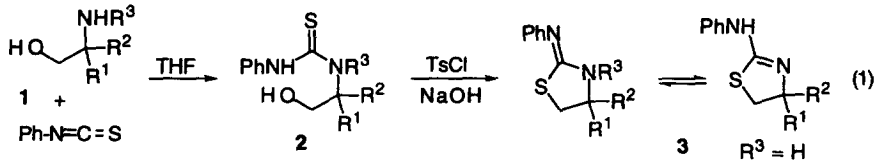


Scheme 1.

N-(2-Hydroxyethyl)thioureas **2** were readily obtained in high yields from the reaction of the corresponding 1,2-aminoalcohols with phenyl isothiocyanate, which provided exclusively the desired products under mild conditions, thus avoiding the need for *O*-protection (Table 1).[9] A survey of one-pot reactions by the combination of TsCl (1.1 equiv.) with various basic metallic (*t*-BuOK, NaOH, and NaH) or non-metallic (Et_3N and Et_3N/DMAP) reagents were performed to **2a** in THF.

In the present reaction, the use of NaOH was found to be most effective in producing 2-

Table 1
One-pot reaction of *N*-(2-hydroxyethyl)thioureas **2**



Entry	R^1	R^2	R^3	Yield (%)[a] of **2**	mp (°C) of **2**	Yield (%)[b] of **3**	mp (°C) of **3**
a	Me	Me	H	71	127-128	94	114-116
b	Me	H	H	98	83-84	77	104-105
c	Et	H	H	99	145-146	78	98-100
d	(S)-$PhCH_2$	H	H	86	103-104	70	oil
e	(S)-*i*-Pr	H	H	85[b]	93-95	79	68-70
f	H	H	Me	93	134-135	29(40)[c]	88-89
g	H	H	Et	91	158-159	27(72)[c]	oil
h	H	H	H	95	138-139	[d]	-

[a]Recrystallized yields and recrystallized solvents were as follows: **2a**, **2c**, toluene; **2b**, **2d**, n-hexane/acetone; **2f**, n-hexane; **2g**, **2h**, chloroform/acetone.
[b]Isolated yields by column chromatography.
[c]Use of Et_3N instead of NaOH gave more improved yields.
[d]The chlorinated thiourea was mainly obtained in 64 % yield.

phenylaminothiazoline **3a**.[10] The NaOH was added to a mixture of the TsCl and **2a** at room temperature. The reactions were complete within 30 min at room temperature.

The one-pot reaction of various substrates **2a–2h** was examined and the results are shown in Table 1. With thioureas **2a–2e** prepared from *N*-unsubstituted aminoalcohols (R^3=H), *S*-cyclization to 2-phenylaminothiazolines was mainly observed with trace amount of the *N*-cyclized products. Thus, all reactions proceeded in good yields with regiocontrol (*S*-cyclization>*N*-cylization) to give 2-phenylaminothiazolines, 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 29/54 and 27/65, respectively. Thiourea **2h** prepared from 2-aminoethanol gave mainly the chlorinated thiourea in 64% yield, containing a small amount of tosylate (6% yield). To improve the yields of *S*-cyclized products in the case of **2f** and **2g**, various bases employed above were also applied to **2g** in THF. Contrary to above result, the refluxed reaction in the presence of 5 equiv. of Et_3N gave most effectively *S*-cyclized product with almost complete regioselectivity. With thiourea **2f** using Et_3N also afforded *S*-cyclized product in 40% improved yield. Although further investigation is needed to understand this reaction, the *S*-cyclization selectivity is remarkably affected by the base employed depending on the nucleophilicity of thioureas.

In conclusion, we have succeeded in the development of a mild synthetic method for 2-phenylaminothiazolines from the corresponding 1,2-aminoalcohols using one-pot reaction with TsCl/NaOH or Et_3N.

Acknowledgements

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9. Synthesis of *N*-[(1,1-dimethyl-2-hydroxy)ethyl]-*N'*-phenylthiourea (**2a**): To a stirred solution of 2-amino-2-methyl-1-propanol **1a** (0.44 mL, 4.59 mmol, 110 M%) in THF (10 mL) under nitrogen at room temperature was added a solution of phenyl isothiocyanate (0.50 mL, 4.18 mmol, 100 M%) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min and evaporated. The crude product was recrystallized in toluene (30 mL) to give **2a** (0.67

g, 71% yield). IR ($CDCl_3$, cm^{-1}) 3262, 1278; ^1H NMR (300 MHz, $CDCl_3$) 7.23–7.43 (5H, m), 6.16 (1H, bs), 3.79 (2H, s), 1.40 (6H, s).

10. Synthesis of 4,5-dihydro-4,4-dimethyl-*N*-phenyl-2-thiazolamine (**3a**): To a stirred solution thiourea **2a** (0.2 g, 0.88 mmol, 100 M%) in THF (10 mL) under nitrogen at room temperature was added a solution of NaOH (88 mg, 2.2 mmol, 250 M%) in water (3 mL) and TsCl (0.18 g, 0.97 mmol, 110 M%) 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 **3a** (0.17 g, 94% yield). IR ($CDCl_3$, cm^{-1}) 1687, 1587; ^1H NMR (300 MHz, $CDCl_3$) 6.93–7.25 (5H, m), 4.02 (2H, s), 1.33 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 28.0, 61.1, 78.7, 120.7, 122.2, 128.7, 156.0; HRMS (EI) calcd for $C_{11}H_{14}N_2S$ 206.0878, found 206.0864.