Solid-Phase Synthesis of 2-Amino-2-thiazolines by the Cyclization of *N*-(2-Hydroxyethyl)thioureas Using TFA

Hyun-Suk Jeon, Quynh Pham Bao Nguyen, Jae Nyoung Kim,† and Taek Hyeon Kim*

*Department of Applied Chemistry and Center for Functional Nano Fine Chemicals, Chonnam National University, Gwangju 500-757, Korea. *E-mail: thkim@chonnam.ac.kr*
†Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
Received July 19, 2007

Key Words : 2-Amino-2-thiazolines, Solid-phase synthesis, *N*-(2-Hydroxyethyl)thioureas

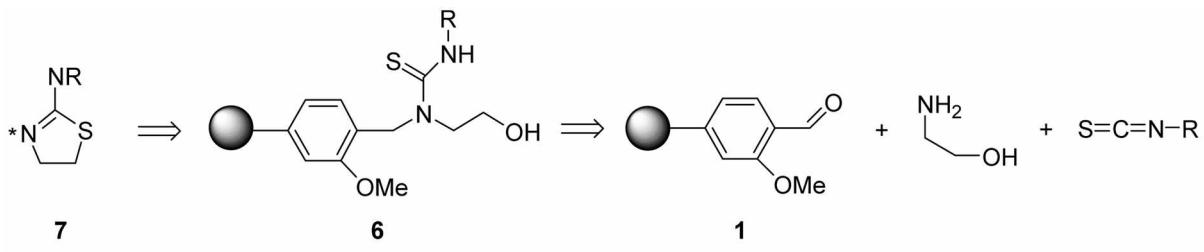
The 2-amono-2-thiazolines have recently gained significant interest as a scaffold that is applicable to the development of bioactive compounds such as pronounced antidepressant agents,[1] potent human nitric oxide synthase inhibitors,[2] octopaminergic-agonists,[3] anthelmintics,[4] and anti-inflammatory agents.[5] The solid phase synthesis of small heterocycles have been considerably studied because it can be applied to the rapid generation of diverse libraries of drug-like compounds.[6] Although there are many well-established reports on the solution phase synthesis of 2-amino-2-thiazolines scaffolds because of their valuable pharmaceutical properties,[3a,3b,7] very recently we first reported a solid phase synthetic method of 2-amino-2-thiazolines from the cyclization of *N*-(2-hydroxyethyl)thioureas using dicyclohexylcarbodiimide (DCC).[8] The ring closure of *N*-(2-hydroxyethyl)thioureas can furnish different products depending on the reaction conditions and substrates such as *S*-cyclized,[7a] *N*-cyclized, or *O*-cyclized[9] products. Resin-bound substrates **6** were designed as precursors to generate 2-amino-2-thiazolines by the S-cyclization, which were conveniently prepared from various commercially available aminoalcohols and isothiocyanates (Scheme 1). We wish to report an alternative and more effective way into the solid phase synthesis of 2-amino-2-thiazolines, using the cyclization of *N*-(2-hydroxyethyl)thioureas.

Scheme 2 shows the synthetic route of the 2-amino-2-thiazoline scaffold. The first step in solid phase reactions was the coupling of amino alcohol onto an ArgoGel-MB-CHO resin[10] *via* reductive amination, followed by the protection of the free alcohol **3** with *tert*-butyldimethylsilyl chloride (TBSCl) according to the previous procedures.[11] Treatment of this intermediate with isothiocyanates afforded the thioureas resin **5**, and subsequent deprotection of the silylated hydroxy group with tetrabutyl ammonium fluoride in THF yielded resin **6**. The intramolecular cyclization of resin **6** using dicyclohexylcarbodiimide (DCC) gave mainly the required S-cyclized 2-amino-2-thiazolines resin **7** as reported.[8] Then we turned to release the *N*-(2-hydroxyethyl)thioureas from the resin **6**, key intermediate in Scheme 2, by the trifluoroacetic acid (TFA) cleavage to determine the loading capacity of the both amino alcohols and isothiocyanates. The desired thiourea was not obtained but the final product 2-amino-2-thiazoline was released in high yield and purity. This is that the cyclization and cleavage reaction in TFA simultaneously occurred at the same step, thereby saving one step procedure. The results using TFA for the cyclization and cleavage are summarized in Table 1. Resin **6** derived from either aliphatic (entry **7a-b**) or aryl isothiocyanates (entry **7c-7k**) furnished the required S-alkylation products, but aminoalcohol was limited to the primary alcohol.[12]

In summary, a solid phase synthetic method was developed for the parallel synthesis of 2-amino-2-thiazolines, using the cyclization of *N*-(2-hydroxyethyl)thioureas and cleavage in TFA. This synthetic methodology is ideally suited for the automated applications, because all the reactions were carried out under ambient conditions.

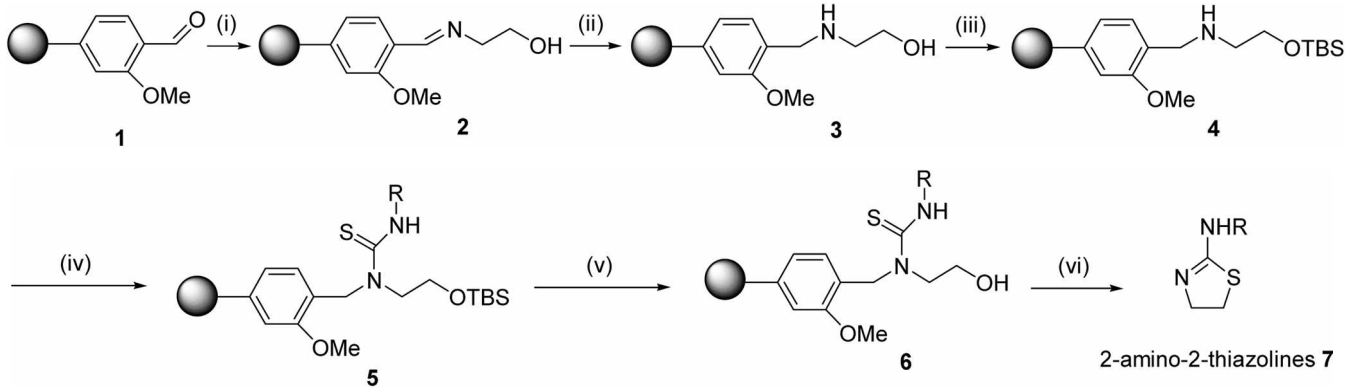
Experimental Section

General synthetic approach of 2-amino-2-thiazolines: The coupling of the ethanolamine (2.0 equiv) to ArgoGel-MB-CHO resin (0.1 mmol), which had been swollen with trimethylorthoformate/MeOH = 4/1 (5 mL), *via* reductive



* Solid support attachment point

Scheme 1



Scheme 2. Solid phase synthetic approach to 2-amino-2-thiazolines. Reagents and conditions: (i) trimethylorthoformate/MeOH=1/4, $H_2NCH_2CH_2OH$ (2 equiv), 24 h; (ii) borane-pyridine complex (3 equiv), AcOH (3 equiv), 24 h; (iii) TBSCl (3 equiv), DMAP (0.1 equiv), TEA (3 equiv); (iv) RNCS (5 equiv), THF; (v) tetrabutyl ammonium fluoride (5 equiv), THF; (vi) 95% TFA/H_2O, 4 h.

Table 1. Synthesis of 2-amino-2-thiazoline derivatives (**7a-k**) from the solid phase as outlined in Scheme **2**

Entry	R	Yield (%)[a]	Purity (%)[b]
7a	Me	66	99
7b	*i*-Pr	34	99
7c	C_6H_5	72[c]	72
7d	4-MeC_6H_4	89	79
7e	4-ClC_6H_4	76	89
7f	3-$CF_3C_6H_4$	72	80
7g	4-CNC_6H_4	80	83
7h	3,4-$Cl_2C_6H_3$	93	83
7i	2-Cl, 4-$NO_2C_6H_3$	75	72
7j	2-MeO, 4-$NO_2C_6H_3$	88	83
7k	2-MeO, 5-MeC_6H_3	67	89

[a]Overall yields from the ArgoGel-MB-CHO resin 1 having loading capacity of 0.41 mmole/g. [b]Purity was determined by HPLC after short-pass silica gel column chromatography. [c]Mp of free base, 151-152 °C (lit.[13] mp 150-152 °C).

amination using borane-pyridine in acetic acid, followed by protection of the free alcohol with TBSCl, gave the silylated resin **4** according to the previous method.[10] The dried resin **4** in dry tetrahydrofuran (5 mL) was then reacted with 2-methoxy-4-nitrophenyl isothiocyanate (5 equiv) for 24 h. The resulting resin was washed thoroughly with DMF (3 × 5 mL), MeOH (3 × 5 mL), THF (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried in vacuum to give resin **5**. The deprotection of the silyl group in resin **5** with tetrabutyl ammonium fluoride (5 equiv) was carried out for 15 h, washed with the same solvent system and dried in vacuum for 30 min. Finally, the dried resin **6** was cyclized and cleaved in a 95% TFA/H_2O solution (5 mL). The cleavage solution was collected by filtration, dried by evaporation and analyzed by HPLC. Spectroscopic data for the final products (compounds were characterized as TFA salts).

Compound **7a**: R_f = 0.2 (ethyl acetate); ESMS ($M+H^+$) 117.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (t, 2H, J = 7.5 Hz), 3.43 (t, 2H, J = 7.5 Hz), 3.00 (s, 3H).

Compound **7b**: R_f = 0.1 (ethyl acetate); ESMS ($M+H^+$) 145.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (bs, 2H), 3.65 (m, 1H), 3.51 (bs, 2H), 1.36 (d, 3H, J = 6.2 Hz), 1.30 (d, 3H, J = 6.2 Hz).

Compound **7c**: R_f = 0.5 (ethyl acetate); ESMS ($M+H^+$) 179.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.19 (m, 5H), 4.08 (t, 2H, J = 7.8 Hz), 3.50 (t, 2H, J = 7.8 Hz).

Compound **7d**: R_f = 0.2 (ethyl acetate); ESMS ($M+H^+$) 193.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (bs, 4H), 4.04 (t, 2H, J = 7.5 Hz), 3.46 (t, 2H, J = 7.5 Hz), 2.36 (s, 3H).

Compound **7e**: R_f = 0.7 (ethyl acetate); ESMS ($M+H^+$) 213.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.08 (m, 2H), 3.86 (bs, 2H), 3.38 (t, 2H, J = 6.8 Hz).

Compound **7f**: R_f = 0.7 (ethyl acetate); ESMS ($M+H^+$) 247.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.08 (m, 2H), 3.86 (bs, 2H), 3.38 (t, 2H, J = 6.8 Hz).

Compound **7g**: R_f = 0.8 (ethyl acetate); ESMS ($M+H^+$) 204.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.40 (m, 2H), 4.06 (bs, 2H, J = 7.6 Hz), 3.57 (t, 2H, J = 7.6 Hz).

Compound **7h**: R_f = 0.5 (ethyl acetate); ESMS ($M+H^+$) 247.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.19 (m, 3H), 4.10 (bs, 2H, J = 7.7 Hz), 3.56 (t, 2H, J = 7.7 Hz).

Compound **7i**: R_f = 0.7 (ethyl acetate); ESMS ($M+H^+$) 258.3; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 1H, J = 2.5 Hz), 8.22 (dd, 1H, J = 8.7, 2.5 Hz), 7.59 (t, 1H, J = 8.8 Hz), 4.26 (t, 2H, J = 7.7 Hz), 3.63 (t, 2H, J = 7.7 Hz).

Compound **7j**: R_f = 0.6 (ethyl acetate); ESMS ($M+H^+$) 254.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, 1H, J = 8.6, 2.0 Hz), 7.83 (d, 1H, J = 2.0 Hz), 7.45 (d, 1H, J = 8.6 Hz), 4.17 (t, 2H, J = 7.7 Hz), 3.99 (s, 3H), 3.57 (t, 2H, J = 7.7 Hz).

Compound **7k**: R_f = 0.2 (ethyl acetate); ESMS ($M+H^+$) 223.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 3H), 4.11 (t, 2H, J = 7.4 Hz), 3.38 (t, 2H, J = 7.4 Hz), 2.29 (s, 3H).

Acknowledgment. This work was supported by the Regional Technology Innovation Program of the Ministry of Commerce, Industry and Energy (grant No. RTI 04-03-03). The spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

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