Report

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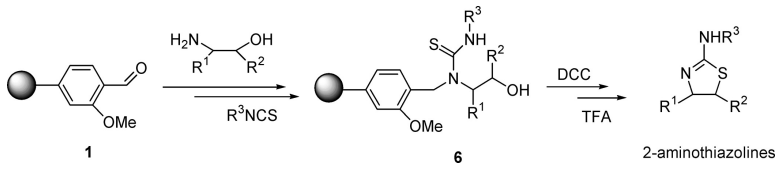

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Reports

Solid-Phase Synthesis of 2-Amino-2-thiazolines from *N*-(2-Hydroxyethyl)thioureas Using 1,3-Dicyclohexylcarbodiimide

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The 2-amino-2-thiazoline ring system has attracted 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 is receiving considerable attention because it can be applied to the rapid generation of diverse libraries of drug-like compounds.[6] Although there are many reports on the solution-phase synthesis of 2-amino-2-thiazoline scaffolds because of their valuable pharmaceutical properties,[3a,3b,7] a route using the solid-phase has not been developed. Here, we report the solid-phase synthesis of 2-amino-2-thiazolines, which can be used for the high-throughput synthesis of drug libraries for potential drug discovery.

The cyclization of *N*-(2-hydroxyethyl)thioureas can provide different products depending on the reaction conditions and substrates such as S-cyclized,[7a] N-cyclized, or O-cyclized[8] products. Recently, a concise procedure to obtain 2-amino-2-thiazolines was developed on the basis of the S-cyclization from *N*-(2-hydroxyethyl)thioureas under Mitsunobu conditions (triphenylphosphine and diethyl azodicarboxylate) in the solution-phase.[7g] The cyclization of resin-attached *N*-(2-hydroxyethyl)thioureas has been extended to a solid-phase synthesis protocol for 2-amino-2-thiazolines. Resin-bound substrates, **6**, were designed as precursors to generate 2-amino-2-thiazolines, which were conveniently prepared from various commercially available aminoalcohols and isothiocyanates for diversity generation.

Table 1. Synthesis of 2-Amino-2-thiazoline Derivatives (**8a**−**o**) from the Solid-Phase as Outlined in Scheme 1

entry	R^1	R^2	R^3	yield (%)[a]	purity (%)[b]
8a	H	H	Me	36	89
8b	H	H	*i*-Pr	34	95
8c	H	H	C_6H_5	63[c]	95
8d	H	H	4-MeC_6H_4	50	96
8e	H	H	4-$MeOC_6H_4$	54	57
8f	H	H	4-$NO_2C_6H_4$	39	95
8g	H	H	4-ClC_6H_4	39	76
8h	H	H	3-$CF_3C_6H_4$	40	82
8i	H	H	4-CNC_6H_4	39	83
8j	H	H	3,4-$Cl_2C_6H_3$	34	85
8k	H	H	2-Cl, 4-$NO_2C_6H_3$	67	94
8l	H	H	2-MeO, 4-$NO_2C_6H_3$	66	80
8m	H	H	2-MeO, 5-MeC_6H_3	67	89
8n	Me	H	4-CNC_6H_4	49	86
8o	(*S*)-*i*-Pr	H	4-CNC_6H_4	65	83

[a] Overall yields from the ArgoGel-MB-CHO resin **1** with a loading capacity of 0.41 mmol/g. [b] Purity was determined by HPLC after short-pass silica gel column chromatography. [c] M_p of free base, 151−152 °C (ref 15, mp = 150−152 °C).

Scheme 1 shows the synthetic route of the 2-amino-2-thiazoline scaffold. The first step in solid-phase reaction was the coupling of various amino alcohols onto an ArgoGel-MB-CHO resin[9] via reductive amination, followed by the protection of the free alcohol **3** with *tert*-butyldimethylsilyl chloride (TBSCl), according to the previous procedures.[10] Treatment of this intermediate with isothiocyanates yielded

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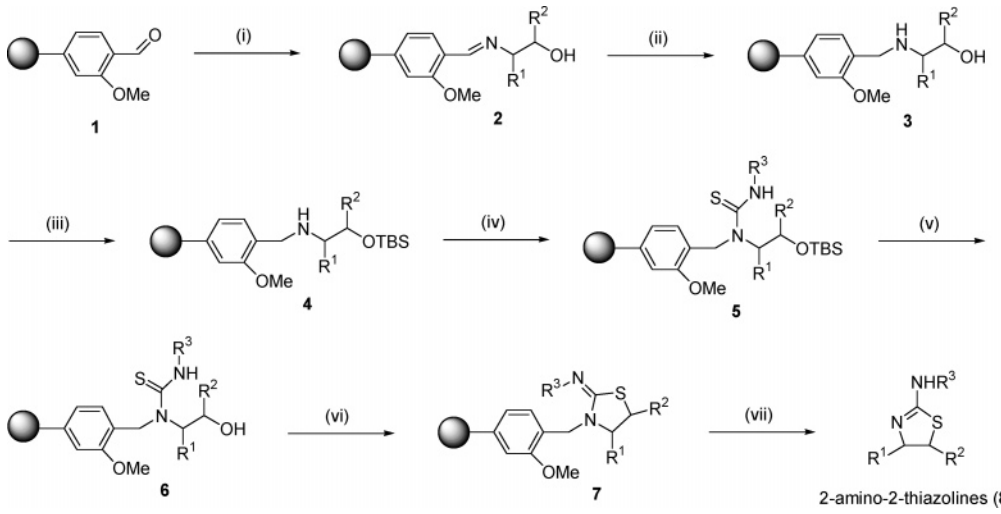
Scheme 1. Solid-Phase Synthesis Approach to 2-Amino-2-thiazolines[a]



[a] Reagents and conditions: (i) trimethylorthoformate/MeOH = 1/4, $H_2NCH(R^1)CH(R^2)OH$ (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) R^3NCS (5 equiv), THF; (v) tetrabutyl ammonium fluoride (5 equiv), THF; (vi) DCC (5 equiv), CH_2Cl_2, o/n; (vii) 95% TFA/H_2O, 4 h.

the thioureas resin **5**, and subsequent deprotection of the silylated hydroxy group with tetrabutyl ammonium fluoride in THF yielded resin **6**. The key reaction step in this scheme, the intramolecular cyclization of resin **6** under Mitsunobu conditions, produced the N-cyclized products,[11] which were not expected in the solution phase. However, dicyclohexylcarbodiimide (DCC) gave mainly the required S-cyclized 2-amino-2-thiazolines resin **7**.[12] The desired 2-amino-2-thiazolines were released at 95% TFA (in H_2O) cleavage for 4 h in high yield and purity and were characterized by the spectroscopic methods.[13] The results are summarized in Table 1. Resin **6** derived from either aliphatic (entry **8a** and **8b**) or aryl isothiocyanates (entries **8c**−**8o**) furnished the required S-alkylation products, but the aminoalcohol was limited to the primary alcohol.[14]

In summary, a solid-phase synthetic method was developed for the parallel synthesis of a wide range of disubstituted 2-amino-2-thiazolines using aminoalcohols and isothiocyanates. The final products were obtained in seven steps in high purity with moderate to good yield. This synthetic methodology is ideally suited for automated applications because all the reactions were carried out under ambient conditions.

The typical synthetic approach of 2-amino-2-thiazolines is as follows: For the synthesis of 4,5-dihydro-*N*-(2-methoxy-4-nitrophenyl)-2-thiazolamine **8l**, 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 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.[9] 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. Resin **6** in CH_2Cl_2 (5 mL) was incubated in DCC (5 equiv) for 24 h and washed thoroughly to give resin **7**. Finally, the dried resin was cleaved in a 95% TFA/H_2O solution (5 mL). The cleavage solution was collected by filtration, dried by evaporation and analyzed by HPLC to a purity of 80%: R_f = 0.6 (ethyl acetate); ESMS ($M + H^+$) 254.1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 2.4, 8.7 Hz), 7.83 (d, 1H, J = 2.4), 7.45 (d, 1H, J = 8.7 Hz), 4.14 (t, 2H, J = 7.7 Hz), 3.99 (s, 3H), 3.55 (t, 2H, J = 7.7 Hz).

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(9) ArgoGel-MB-CHO resin was purchased from Argonaut Technologies Inc.

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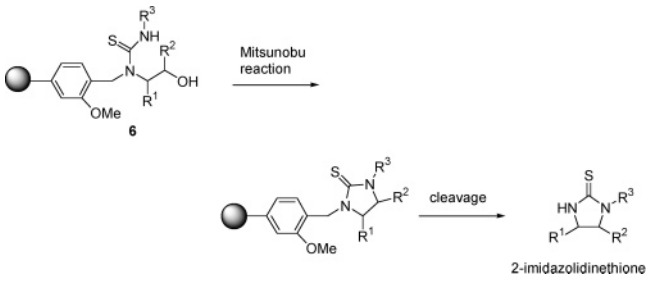
(11) The N-cyclized compound, 2-imidazolidinethione, will be developed as a library in the future.



(12) You and co-worker reported that the cyclization of *N*-(2-hydroxyethyl)thioureas-mediated DCC in solution-phase gave O-cyclized products, 2-amino-2-oxazolines.[8b]

(13) Spectroscopic data for the final products (compounds were characterized as TFA salts). **8a**: 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). **8b**: 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). **8c**: 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). **8d**: 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). **8e**: R_f = 0.1 (ethyl acetate); ESMS (M + H$^+$) 209.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 2H), 6.92 (m, 2H), 4.15 (t, 2H, J = 7.7 Hz), 3.83 (s, 3H), 3.50 (t, 2H, J = 7.7 Hz). **8f**: R_f = 0.7 (ethyl acetate); ESMS (M + H$^+$) 224.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.51 (m, 2H), 4.17 (t, 2H, J = 7.8 Hz), 3.65 (t, 2H, J = 7.8 Hz). **8g**: 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), 3.375 (t, 2H, J = 6.8 Hz). **8h**: 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), 3.375 (t, 2H, J = 6.8 Hz). **8i**: 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). **8j**: 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). **8k**: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 = 2.5, 8.7), 7.59 (t, 1H, J = 8.8 Hz), 4.26 (t, 2H, J = 7.7 Hz), 3.63 (t, 2H, J = 7.7 Hz). **8m**: 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). **8n**: R_f = 0.6 (ethyl acetate); ESMS (M + H$^+$) 218.3; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, 2H, J = 1.8, 5.5 Hz), 7.45 (dd, 2H, J = 1.8, 5.1 Hz), 4.58 (m, 1H), 3.71 (m, 1H), 3.24 (m, 1H), 1.54 (d, 3H, J = 6.3 Hz). **8o**: R_f = 0.6 (ethyl acetate); ESMS (M + H$^+$) 246.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 4.24 (m, 1H), 3.60 (m, 1H), 3.36 (m, 1H), 2.10 (m, 1H), 1.04 (d, 6H, J = 6.8 Hz).

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