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Novel Synthesis of Dihydrothiazoles from the Selenium-Induced Cyclization of Allyl Thioureas

Hao Qian [a] & Yanhong Lian [a b]
[a] Department of Chemistry , Hangzhou Normal University , Hangzhou, China
[b] Department of Anaesthesia , Zhejiang Cancer Hospital , Hangzhou, China
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Novel Synthesis of Dihydrothiazoles from the Selenium-Induced Cyclization of Allyl Thioureas

Hao Qian[1] and Yanhong Lian[1,2]

[1]Department of Chemistry, Hangzhou Normal University, Hangzhou, China
[2]Department of Anaesthesia, Zhejiang Cancer Hospital, Hangzhou, China

Abstract: The reaction of allylic thioureas with phenylselenenyl chloride affords 2-amino dihydrothiazoles in excellent yields by selenium-induced cyclization of allylic thioureas.

Keywords: allylic thiourea, cyclization, dihydrothiazole, phenylselenenyl chloride

The 2-amino dihydrothiazole 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,[3,4] anthelmintics,[5] and anti-inflammatory agents.[6] There are many reports on the synthesis of 2-amino dihydrothiazole scaffolds because of their valuable pharmaceutical properties.[3,7,8] These compounds are usually prepared by the hydrochloric acid–catalyzed cyclization of N-(2-hydroxyethyl)-thiourea derivatives[3,5,8c] or the cyclization of hydrogen sulfate of thiourea derivatives[3,8a] in aqueous basic conditions. These methods give low yields for the formation of the 2-amino dihydrothiazoles and are not applicable to acid-sensitive or

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Address correspondence to Hao Qian, Department of Chemistry, Hangzhou Normal University, 521 Mail Box, Hangzhou 310036, China. E-mail: qianhao@hznu.edu.cn

racemization-prone substrates because of the vigorous acidic or basic reaction conditions.

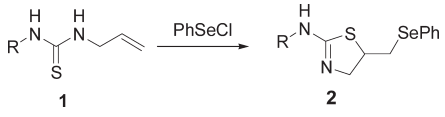
Phenylselenofunctionalization reactions (i.e., the phenylselenium-induced cyclization of alkenes bearing an internal nucleophile) is a well-known chemical procedure. Since the first example described, the selenolactonization of 4-pentenoic acid, organoselenium-induced cyclization reaction have been widely explored in organic synthesis over the past decade because, depending on the nature of the internal nucleophile, a variety of five- and six-membered ring heterocycles can be prepared. In many respects, selenocyclofunctionalization can be comparable to the corresponding halo-or thiocyclization. However, the selenium protocol has the advantage that the introduction of the heteroatom, the manipulation of the obtained product, and the removal of the function are facilitated by the simple and milder conditions required, such as oxidation, syn-selenoxide elimination, hydrogenolytic removal, or nucleophilic substitution of the corresponding selenones.[9] Our research group has been interested in the application of organoselenium reagents in organic synthesis.[10] Here, we report an efficient and convenient method for synthesis of 2-amino dihydrothiazoles in high yields by selenium-induced intramolecular functionalization of allylic thioureas (Scheme 1).

When allylic thioureas were treated in dry chloroform at room temperature with a stoichiomentric amount of phenylselenenyl chloride, 2-amino dihydrothiazoles were isolated as the only product in excellent yields (Table 1). The formation of the five-membered-ring dihydrothiazoles from allylic thioureas rather than the six-membered dihydrothiazines was established by spectroscopy. In these cases, we observed formation of a heterocycle by sulfur participation instead of by nitrogen participation.

In conclusion, we have succeeded in the development of an efficient and convenient method for synthesis of 2-amino dihydrothiazoles in excellent yields by phenylselenenyl chloride–induced cyclization of allylic thioureas.

EXPERIMENTAL

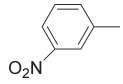
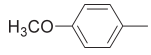
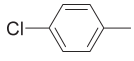
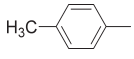
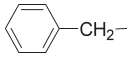
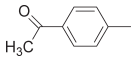
Melting points were recorded on a Kofler melting-point apparatus and are uncorrected. ^{1}H NMR (400 MHz) spectra in $CDCl_3$ were obtained on a Bruker Avance 400 and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded by the electron ionization (EI) method on an



1 2

Scheme 1.

Table 1. Preparation of 2-amino dihydrothiazoles

Products	R	Yield (%)[a]
2a		97
2b		97
2c		96
2d		92
2e		94
2f		95
2g		96
2h		94
2i		93

[a]Based on pure isolated products.

HP5989B mass spectrometer. Microanalysis was carried out on a Carlo Erba 1106. Infrared spectra were recorded using a Bruker Tensor-27 spectrometer. Chloroform was purified by the standard method[11] before use.

General Procedure for the Preparation of 2-Amino Dihydrothiazoles 2a–i

The required allylic thioureas **1** were readily prepared according to the literature procedure.[12] Phenylselenenyl chloride (2 mmol) is rapidly added at 0°C to the allylic thiourea **1** (2 mmol) solution in dry $CHCl_3$ (20 mL). After stirring for 20 min at 0°C, the resulting solution was raised to room temperature and sequentially stirred for 6 h. Usual workup and purification on preparative layer chromatography on silica gel afforded 2-amino dihydrothiazoles **2**.

Data

Compound **2a**. Yield 97%; white solid; mp 110–111°C. IR (KBr): 3443, 3193, 2969, 2857, 1617, 1588, 1325, 1033, 752, 735, 692 cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$): $\delta = 3.16$ (d, *J*, 7.41 Hz, 2H), 3.79–3.89 (m, 3H), 5.08 (s, 1H), 7.03 (m, 1H), 7.10–7.12 (m, 2H), 7.26–7.29 (m, 5H), 7.50–7.52 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 31.81$, 47.95, 54.38, 120.79, 122.87, 127.14, 128.28, 128.48, 128.84, 132.89, 146.51, 160.53. MS (EI, 70 eV): $m/z = 348$ (M^+), 267, 245,191,157, 131, 77, 73. Anal. calcd. for $C_{16}H_{16}N_2SSe$: C, 55.33; H, 4.54; N, 8.07. Found: C, 55.41; H, 4.59; N, 8.10.

Compound **2b**. Yield 97%; IR (KBr): 3440, 3062, 2921, 2853, 1649, 1595, 1477, 1214, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H), 3.16 (d, *J*, 7.06 Hz, 2H), 3.62 (d, *J*, 8.20 Hz, 1H), 3.71–3.78 (m, 2H), 7.02–7.05 (m, 2H), 7.14–7.20 (m, 2H), 7.29 (m, 3H), 7.51 (m, 2H), 7.69 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 18.04$, 32.23, 47.63, 52.97, 122.22, 123.99, 126.49, 127.66, 129.43, 130.40, 130.60, 133.40, 135.72, 147.40, 161.83. MS (EI, 70 eV): $m/z = 363$ (M^+), 347, 281, 249, 205, 189,157, 91, 77, 73. Anal. calcd. for $C_{17}H_{18}N_2SSe$: C, 56.50; H, 5.02; N, 7.75. Found: C, 56.59; H, 4.96; N, 7.81.

Compound **2c**. Yield 96%; yellow solid; mp 142–143°C. IR (KBr): 3419, 3027, 2923, 2860, 1635, 1603, 1523, 1477, 1350, 1193, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.18$ (d, *J*, 7.53 Hz, 2H), 3.69–3.72 (m, 1H), 3.78–3.82 (m, 1H), 3.85–3.90 (m, 1H), 5.92 (s, 1H), 7.27–7.33 (m, 4H), 7.42 (m, 1H), 7.52 (d, *J*, 7.30 Hz, 2H), 7.89 (d, *J*, 1.87 Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 31.93$, 48.08, 52.46, 116.37, 117.95, 121.20, 127.79,127.86, 128.42, 129.43, 129.62, 133.56, 148.80, 150.01, 162.01. MS (EI, 70 eV): $m/z = 393$ (M^+), 288, 236, 222, 180, 134, 90, 73. Anal. calcd. for $C_{16}H_{15}N_3O_2SSe$: C, 48.98; H, 3.85; N, 10.71. Found: C, 48.90; H, 3.79; N, 10.69.

Compound **2d**. Yield 92%; IR (KBr): 3432, 3260, 3052, 2926, 2855, 1636, 1508, 1384, 1242, 1033, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.15$ (d, *J*, 6.62 Hz, 2H), 3.71–3.83 (m, 3H), 3.77 (s, 3H), 6.82 (d, *J*, 8.63 Hz, 2H), 7.00 (d, *J*, 8.16 Hz, 2H), 7.27–7.32 (m, 3H), 7.50 (m, 2H), 7.58 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 32.30$, 48.29, 54.53, 55.46, 144.19, 122.78, 124.63, 127.66, 128.74, 129.44, 133.38, 135.80, 140.27, 156.00, 161.49. MS (EI, 70 eV): $m/z = 378$ (M^+), 313, 297, 254, 221, 155,122, 77, 73. Anal. calcd. for $C_{17}H_{18}N_2OSSe$: C, 54.11; H, 4.81; N, 7.42. Found: C, 54.02; H, 4.75; N, 7.44.

Compound **2e**. Yield 94%; IR (KBr): 3419, 3157, 3068, 2922, 2860, 1638, 1581, 1477, 1193, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.16$ (d, *J*, 6.32 Hz, 2H), 3.75 (m, 1H), 3.82 (d, *J*, 6.32 Hz, 2H), 6.58 (s, 1H), 6.97–7.01(t, *J*, 7.64 Hz,1H), 7.17–7.21 (t, *J*, 7.75 Hz, 1H), 7.26–7.30 (m, 4H), 7.36 (d, *J*, 7.96 Hz, 1H), 7.50 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 32.13$, 48.19, 54.16, 122.77, 123.33, 124.03, 126.12, 127.37, 127.74, 128.69, 129.35, 129.50, 133.47, 145.14, 161.58. MS (EI, 70 eV): $m/z = 383$ (M^+), 345, 301, 225, 189,157, 91, 73. Anal. calcd. for $C_{16}H_{15}ClN_2SSe$: C, 50.34; H, 3.96; N, 7.34. Found: C, 50.27; H, 3.88; N, 7.38.

Compound **2f**. Yield 95%; IR (KBr): 3441, 3075, 2898, 2854, 1632, 1581, 1481, 1177, 1022, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.13$ (d, *J*, 7.36 Hz, 2H), 3.65–3.69 (m, 1H), 3.73–3.84 (m, 2H), 6.42 (s, 1H), 6.97 (d, *J*, 8.46 Hz, 2H), 7.22 (d, *J*, 8.50 Hz, 2H), 7.26 (m, 3H), 7.49 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 32.13$, 48.08, 53.28, 122.79, 127.76, 128.49, 128.61, 129.03, 129.41, 133.46, 146.55, 161.72. MS (EI, 70 eV): m/z = 383 (M^+), 313, 225, 189,157, 111, 91, 73. Anal. calcd. for $C_{16}H_{15}ClN_2SSe$: C, 50.34; H, 3.96; N, 7.34. Found: C, 50.39; H, 3.89; N, 7.37.

Compound **2g**. Yield 96%; IR (KBr): 3425, 3060, 2920, 2852, 1642, 1606, 1508, 1476, 1214, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H), 3.14 (d, *J*, 6.94 Hz, 2H), 3.74–3.82 (m, 3H), 6.62 (s, 1H), 6.98 (d, *J*, 8.02 Hz, 2H), 7.07 (d, *J*, 7.92 Hz, 2H), 7.25–7.30 (m, 3H), 7.49–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 20.90$, 32.30, 48.44, 54.91, 121.27, 127.67, 128.73, 129.37, 129.42, 129.59, 133.10, 133.42, 135.81, 144.51, 161.04. MS (EI, 70 eV): m/z = 362 (M^+), 281, 222, 205, 157, 145, 132, 91, 77, 73. Anal. calcd. for $C_{17}H_{18}N_2SSe$: C, 56.50; H, 5.02; N, 7.75. Found: C, 56.44; H, 4.96; N, 7.74.

Compound **2h**. Yield 94%; IR (KBr): 3258, 3062, 3032, 2925, 1616, 1578, 1496, 1225, 1072, 739, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.10$ (d, *J*, 7.60 Hz, 2H), 3.89–3.99 (m, 3H), 4.42 (d, *J*, 2.40 Hz, 2H), 5.05 (s, 1H), 7.24–7.33 (m, 8H), 7.50–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 33.11$, 48.94, 52.32, 63.79, 127.31, 127.51, 127.65, 128.41, 128.45, 128.89, 129.12, 133.21, 133.26, 138.26, 160.38. MS (EI, 70 eV): m/z = 362 (M^+), 281, 205, 189, 157, 117, 106, 91, 73. Anal. calcd. for $C_{17}H_{18}N_2SSe$: C, 56.50; H, 5.02; N, 7.75. Found: C, 56.57; H, 4.99; N, 7.80.

Compound **2i**. Yield 93%; IR (KBr): 3307, 3052, 2923, 1670, 1635, 1586, 1537, 1358, 1269, 1176, 736, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.54$ (s, 3H), 3.15 (d, *J*, 7.33 Hz, 2H), 3.71–3.91 (m, 3H), 6.97 (d, *J*, 8.36 Hz, 2H), 7.25–7.28 (m, 3H), 7.49–7.51 (m, 2H), 7.88 (d, *J*, 8.46 Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 26.46$, 29.38, 32.32, 48.89, 120.66, 127.87, 128.69, 129.49, 129.91, 132.24, 133.60, 160.04, 197.16. MS (EI, 70 eV): m/z = 390 (M^+), 375, 345, 276, 233, 217, 203, 191, 173, 157, 145, 130, 117, 106, 91, 73. Anal. calcd. for $C_{18}H_{18}N_2OSSe$: C, 55.52; H, 4.66; N, 7.19. Found: C, 55.46; H, 4.61; N, 7.23.

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