Synthesis of Thiazolines by the Reaction of Aryl Ketonitriles with Cysteamine *via* Microwave Irradiation

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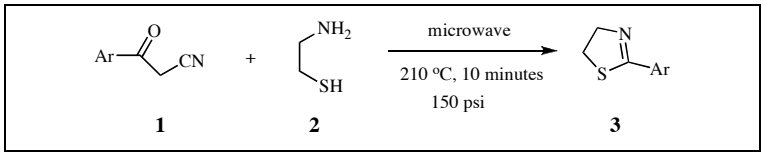

Thiazolines were synthesized in a one-pot reaction in excellent yield using a newly developed methodology. Ketonitriles were directly condensed with cysteamine (2-amino-thioalcohol) *via* microwave irradiation at 210°C for 10 minutes under solvent free conditions and without any solid support. All the compounds were characterized by ^{1}H nmr, ^{13}C nmr spectroscopy and elemental analyses.

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INTRODUCTION

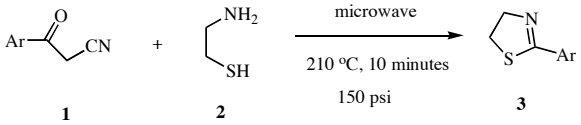
The use of thiazolines building blocks in pharmaceutical drug discovery is continually increasing [1]. Thiazolines are found in numerous interesting biologically active natural products such as *Curacin A*, *Thiangazole, Mirabazole B,* and Lissoclinamides [2]. Moreover, thiazolines constitute a family of compounds known for their application in flavor chemistry [3]. More than 30 thiazoline structures have been identified from natural sources [4], particularly in cooked meat [3] and in certain exotic fruits such as litchis [5]. Some thiazolines derivatives present interesting anti-HIV [6] and anti-cancer [7,8] activities and can inhibit cell division [9].

Consequently, a variety of methods have been reported for the synthesis of thiazoline building blocks, for example (i) the condensation of aminothiols with nitriles [10], esters [11], iminoethers [12], or imino triflates [13], (ii) from *N*-acyl-2-aminoethanols [14] and (R)-hydroxy thioamides [15], (iii) by the multi-step conversion from oxazolines [16] and (iv) by the microwave irradiation of *N*-acylbenzotriazoles with 2-aminoethanethiol hydrochloride [17]. However, these reactions generally require drastic reaction conditions, such as the use of triisobutyl aluminium. Furthermore when nitriles are employed, a Lewis acid is required along with higher temperatures for the elimination of ammonia [10]. Other methods employ complex reagents [15b] or strongly acidic conditions. For example, the preparation of *N*-acyl-benzotriazoles [17] requires triethylamine along with hazardous chemicals such as thionyl chloride. Herein, we report a solvent-free direct synthesis of thiazolines by irradiation of a 1:1 mixture of commercially available cysteamine and an aryl ketonitrile without the use of a solid support or hazardous chemicals.

RESULTS AND DISCUSSION

As shown in Scheme 1, the thiazolines **3** were synthesized in a one pot reaction by the microwave irradiation of a 1:1 mixture of cysteamine (**2**) and the

Scheme 1



appropriate aryl ketonitrile **1** at 210 °C for 10 minutes. The crude reaction mixtures were purified by column chromatography on silica gel using 40% ethyl acetate-hexane as eluent to give, as shown in Table 1, the corresponding thiazoline **3** in good to excellent yields. Irradiation of the reaction mixture above 210 °C or for longer periods of time (> 10 minutes) afforded intractable mixtures. The procedure used was simple; one mixes the two reagents in 1:1 ratio in a microwaveable test tube that is then irradiated at 210 °C for 10 minutes. For comparison, when we carried out the reaction of **1a** with **2** using conventional oil bath heating at 210 °C for 10 minutes, thiazoline **3a** was obtained in a significantly lower yield of 55%. The difference in the thiazoline yields most probably reflects the rapid and volumetric heating in the microwave procedure as compared to the slow superficial heating in the conventional method [18].

The most plausible mechanism (Scheme 2) involves either nucleophilic attack by the thiol group of cystamine onto the carbonyl carbon of ketonitrile forming adduct **4**. The elimination of water from **4** yields the aminonitrile

Table 1

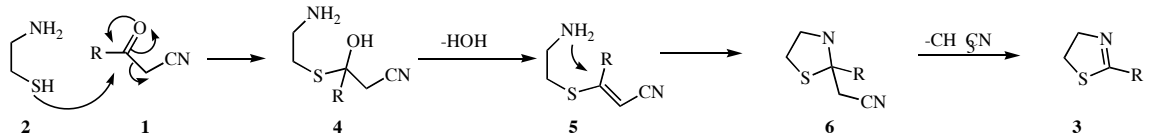
Synthesis of Thiazolines

Entry	1	Ar	3	Yield, %[a]
1	**a**	C_6H_5	**a**	93
2	**b**	4-F-C_6H_4	**b**	93
3	**c**	4-Cl-C_6H_4	**c**	98
4	**d**	4-Me-C_6H_4	**d**	89
5	**e**	4-MeO-C_6H_4	**e**	98
6	**f**	Naphth-1-yl	**f**	96
7	**g**	2,4-diMeO-C_6H_3	**g**	91
8	**h**	2,4-di-Cl-C_6H_3	**h**	96
9	**i**	3,4,5-tri-MeO-C_6H_3	**i**	92
10	**j**	4-CN-C_6H_4	**j**	85
11	**k**	4-Br-C_6H_4	**k**	97

[a] Isolated yield

5 which undergoes intra-molecular conjugate addition of the amino group onto the nitrile **5** to give **6**. Compound **6** then loses acetonitrile to give the product **3**. The

Scheme 2



formation of acetonitrile was confirmed by GC/MS analysis of the crude reaction mixture. The proposed mechanism is consistent with that reported previously [19].

In conclusion, we have developed a new high yield solvent-free one-pot synthesis of biologically important thiazolines that are otherwise not possible by previous methods described in the literature. This successful use of microwave irradiation provides a good example of green synthesis for biologically important organic molecule.

EXPERIMENTAL

Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C nmr spectra were recorded on a 400 MHz Bruker ADVANCE DRX-400 Multinuclear nmr spectrometer. Chemical shifts are reported in reference to TMS as internal standard. GC/MS experiment was done in HP Gas Chromatograph Electron Ionization Detector (GCD System, G1800C). Elemental analysis was obtained from Southern Methodist University Analytical Service Laboratories. All chemicals were purchased from Fisher Scientific or Aldrich chemicals. Microwave experiment was done in CEM-Discover (From CEM Corporation, POB 200) instrument at 150 W output power.

General Procedure for the Synthesis of Compounds 3a- 3l via Microwave Irradiation: A mixture of cystamine (200 mg, 1.6 mmol) and aryl ketonitrile (1 equivalent, 1.6 mmol) were taken in a sealed microwavable test tube and irradiate the mixture at 210 °C for 10 minutes at 150 W output. The reaction mixture was purified by column chromatography using 40% ethyl acetate-hexane as eluent. The results are shown below.

2-Phenylthizoline (3a). This compound was isolated as a yellow gummy liquid [20]. ^{1}H nmr (deuteriochloroform): 3.41 (t, J= 8.3 Hz, 2H, CH_2), 4.46 (t, J = 8.2 Hz, 2H, CH_2), 7.40-7.46 (m, 3H, phenyl hydrogens), 7.85 (d, J = 7.0 Hz, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 34.0 (CH_2), 65.6(CH_2), 128.7 (CH), 128.8(CH), 131.5(CH), 133.6 (C), 168.8(C). *Anal.* Calcd for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58. Found: C, 66.25; H, 5.58; N, 8.59.

2-(4-Fluorophenyl)thiazoline (3b). This compound was isolated as a yellow oil. ^{1}H nmr (deuteriochloroform): 3.42 (t, J = 8.2 Hz, 2H, CH_2), 4.44 (t, J = 8.2 Hz, 2H, CH_2), 7.09 (d, J = 8.1 Hz, 2H, phenyl hydrogens), 7.83 (d, J = 8.1 Hz, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 34.3(CH_2), 65.6(CH_2), 115.8(CH), 116.0(CH), 129.9(CH), 130.7(CH), 130.8(CH), 163.6(C), 166.1(C). *Anal.* Calcd for C_9H_8FNS: C, 59.65; H, 4.45; N, 7.73. Found: C, 60.01; H, 4.48; N, 7.76.

2-(4-Chlorophenyl)thiazoline (3c). This compound was isolated as a yellow solid, mp 51-52 °C (Lit [21] mp 50-51°C). ^{1}H nmr (deuteriochloroform): 3.42 (t, J = 8.3 Hz, 2H, CH_2), 4.45 (t, J = 8.3 Hz, 2H, CH_2), 7.38 (d, J = 8.5 Hz, 2H, phenyl hydrogens), 7.77 (d, J = 8.5 Hz, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 34.3(CH_2), 65.6(CH_2), 129.1(CH), 130.0(CH), 132.1(C), 137.5(C), 167.6(C). *Anal.* Calcd for C_9H_8ClNS: C, 54.68; H, 4.08; N, 7.09. Found: C, 54.69; H, 4.09; N, 7.10.

2-(4-Methylphenyl)thiazoline (3d). This compound was isolated as a yellow solid, mp 40°C (Lit [21] mp 39.5-40.5°C). ^{1}H nmr (deuteriochloroform); 2.39 (s, 3H, CH_3), 3.40 (t, J = 8.3 Hz, 2H, CH_2), 4.45 (t, J = 8.3 Hz, 2H, CH_2), 7.22 (d, J = 8.2 Hz, 2H, phenyl hydrogens), 7.74 (d, J = 8.2 Hz, 2H, phenyl hydrogens). nmr (deuteriochloroform): 21.8(CH_3), 33.9(CH_2), 65.5 (CH_2), 128.7(CH), 129.5(CH), 131.0(C), 141.8(C), 168.7(C). *Anal.* Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90. Found: C, 67.77; H, 6.25; N, 8.01.

2-(4-Methoxyphenyl)thiazoline (3e). This compound was isolated as a light yellow solid, mp 55-56 °C (Lit [21] mp 53.5-54.5 °C). ^{1}H nmr (deuteriochloroform): 3.40 (t, J = 8.3 Hz, 2H, CH_2), 3.85 (s, 3H, -OMe), 4.43 (t, J = 8.3 Hz, 2H, CH_2), 6.92 (d, J = 7.9 Hz, 2H, phenyl hydrogens), 7.79 (d, J = 7.9 Hz, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloro-form): 34.1(CH_2), 55.7 (OMe), 65.4(CH_2), 114.1(CH), 126.4, 130.4(CH), 162.2(C), 168.1(C).

2-Naphthalenethiazoline (3f). This compound was isolated as a yellow gummy liquid. ^{1}H nmr (deuteriochloroform): 3.47 (t, J = 8.3 Hz, 2H, CH_2), 4.53 (t, J = 8.2 Hz, 2H, CH_2), 7.52-7.58

(m, 2H, phenyl hydrogens), 7.87 (d, J = 8.4 Hz, 2H, phenyl hydrogens), 7.93 (d, J = 7.8 Hz, 1H, phenyl hydrogen), 8.03 (d, J = 8.4 Hz, 1H, phenyl hydrogen), 8.28 (s, 1H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 34.1 (CH_2), 65.7(CH_2), 125.1(CH), 127.0(CH), 127.8(CH), 128.1(CH), 128.6(CH), 129.2(CH), 129.8(CH), 131.1(C), 133.2(C), 135.0(C), 168.8(C). *Anal*. Calcd for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57. Found: C, 73.22; H, 5.21; N, 6.58.

2-(2,4-Dimethoxyphenyl)thiazoline (3g). This compound was isolated as a yellow gummy liquid. ^{1}H nmr (deuteriochloroform): 3.35 (t, J = 8.3 Hz, 2H, CH_2), 3.83 (s, 6H, -OMe X 2), 4.44 (t, J = 8.2 Hz, 2H, CH_2). 6.46 (d, J = 8.3 Hz, 1H, phenyl hydrogens), 6.51 (s, 1H, phenyl hydrogen), 7.32 (d, J = 8.3 Hz, 1H, phenyl hydrogen). ^{13}C nmr (deuteriochloroform): 32.1 (CH_2), 55.7 (-OMe), 55.8 (-OMe), 63.3(CH_2), 101.1(CH), 106.0(CH), 116.1(C), 132.3(CH), 161.6(C), 163.5(C), 164.5(C). *Anal*. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.18; H, 5.88; N, 6.28.

2-(2,4-Dichlorophenyl)thiazoline (3h). This compound was isolated as a yellow gummy liquid. ^{1}H nmr (deuteriochloroform): 3.26 (t, J = 8.1 Hz, 2H, CH_2), 4.25 (t, J = 8.1 Hz, 2H, CH_2), 7.13 (d, J = 7.9 Hz, 1H, phenyl hydrogen), 7.30 (s, 1H, phenyl hydrogen), 7.55 (d, J = 7.9 Hz, 1H, phenyl hydrogen). ^{13}C nmr (deuteriochloroform): 32.5(CH_2), 61.5(CH_2), 126.9(CH), 128.5(CH), 131.3(CH), 135.6(C), 135.8(C), 137.2(C), 164.1(C). *Anal*. Calcd for $C_9H_7Cl_2NS$: C, 46.57; H, 3.04; N, 6.03. Found: C, 46.57; H, 3.09; N, 6.06.

2-(3,4,5-Trimethoxyphenyl)thiazoline (3i). This compound was isolated as a yellow gummy liquid. ^{1}H nmr (deuteriochloroform): 3.29 (t, J = 8.4 Hz, 2H, CH_2), 4.41 (t, J = 8.4 Hz, 2H, CH_2), 3.83 (s, 3H, -OMe), 3.85 (s, 6H, -OMe X 2), 6.65 (s, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 33.4(CH_2), 56.3(-OMe), 56.5(-OMe X 2), 63.1(CH_2), 106.1(CH), 106.5(CH), 131.6(C), 135.5(C), 150.1(C), 150.3(C), 163(C). *Anal*. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.95; H, 6.01; N, 5.56.

2-(4-Cyanophenyl)thiazoline (3j). This compound was isolated as a brownish solid, mp 128-130 °C. ^{1}H nmr (deuteriochloroform): 3.25 (t, J = 8.3 Hz, 2H, CH_2), 4.24 (t, J = 8.3 Hz, 2H, CH_2), 7.51 (d, J = 8.3 Hz, 2H, phenyl hydrogens), 7.84 (d, J = 8.3 Hz, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 33.2 (CH_2), 61.5 (CH_2), 113.5(C), 117.1(CN), 129.3(CH), 129.4(CH), 132.1(CH), 132.2(CH), 141.5 (C), 164.5(C). *Anal*. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found C, 63.83; H, 4.29; N, 14.90.

2-(4-Bromophenyl)thiazoline (3k). This compound was isolated as a yellow gummy liquid. ^{1}H nmr (deuteriochloroform): 3.35 (t, J= 8.1 Hz, 2H, CH_2), 4.24 (t, *J*=8.2 Hz, 2H, CH_2), 7.31 (d, *J*=8.2 Hz, 2H, phenyl hydrogens), 7.55 (d, *J* =8.2 Hz, 2H, phenyl hydrogens). ^{13}C nmr (deuteriochloroform): 33.1(CH_2), 63.2(CH_2), 124.1(C), 131.1(CH), 131.3 (CH), 131.8(CH), 131.9(CH), 136.5(C), 163.5(C). *Anal*. Calcd for C_9H_8BrNS: C, 44.64; H, 3.33; N, 5.78. Found: C, 44.66; H, 3.34; N, 5.58.

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