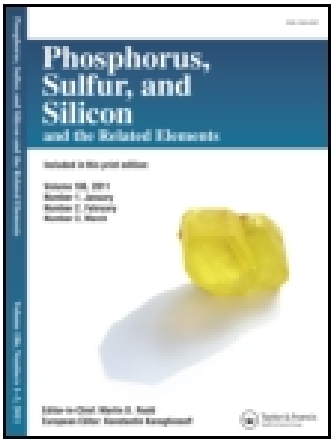

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ONE-POT SYNTHESIS OF 2-ARYLTHIAZOLINES WITH 1-BUTYL-3-METHYLIMIDAZOLIUM TRIBROMIDE AS A CATALYTIC REAGENT

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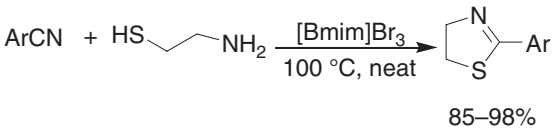
GRAPHICAL ABSTRACT



Abstract *A simple, inexpensive, and efficient one-pot synthesis of 2-arylthiazoline derivatives under solvent-free conditions using a catalytic amount of 1-butyl-3-methylimidazolium tribromide with excellent product yields is reported. This methodology provides easy, quantitative access to various 2-arylthiazoline derivatives, using environmentally benign 1-butyl-3-methylimidazolium tribromide as a catalyst.*

Keywords 2-Arylthiazolines; 2-aminoethanethiol; nitriles; 1-butyl-3-methylimidazolium tribromide; solvent-free synthesis

INTRODUCTION

2-Thiazolines are a class of *N*-heterocycles that have attracted much attention because of their broad range of pharmacological activities such as antibiotic,[1] antitumor,[2] antimalarial,[3] antiproliferative,[4] and anti-HIV.[5] Several methods have been reported for the synthesis of 2-substituted thiazolines including reactions of 2-aminoethanethiol with different precursors such as carboxylic acids,[6] esters,[7] nitriles,[8] *N*-acylbenzotriazoles,[9] lanthanide amino alkoxide,[10] and aldehydes.[11] Although these methods are valuable, but most of them are associated with different drawbacks such as long reaction time, low yields, strongly acidic conditions, and use of expensive reagents. Therefore, there is still a need to develop a simple and convenient approach for the preparation of 2-substituted thiazolines.

During recent years, ionic liquids have attracted interest as environmentally benign reagents due to their favorable properties and a variety of catalytic reactions have been successful using ionic liquids.[12] The solvophobic properties of ionic liquids are able to generate an internal pressure and promote the association of the reactants in a solvent

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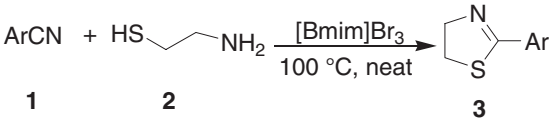
cavity during the activation process and accelerate a reaction. This property of ionic liquids is very efficient for multicomponent reactions in which the entropy of reaction is decreased in the transition state. 1-butyl-3-methylimidazolium tribromide ([Bmim]Br_3) is a stable liquid, which can be readily prepared by the reaction of equimolar amounts of 1-butyl-3-methylimidazolium bromide and bromine. This reagent, which can be stored for several months without loss of activity, has recently been used for the stereoselective bromination of alkynes, ketones, phenols, and arylamines.[13] Herein, we describe a mild, convenient, and simple procedure by condensation of nitriles with 2-aminoethanethiol for the preparation of 2-substituted thiazolines under solvent-free conditions using environmental [Bmim]Br_3 as a catalyst (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

At the outset, to optimize the reaction conditions, we carried out the reaction of benzonitrile with 2-aminoethanethiol as a model reaction in the presence of different amounts of the catalyst at different temperatures under thermal solvent-free conditions. The results of this study are summarized in Table 1. As shown in Table 1, the best results used 1 mol% of the catalyst at 100 °C.

Next, we applied the optimal protocol to a diverse range of nitriles with 2-aminoethanethiol and studied the scope of this reaction for preparation of varieties of

Table 1 Synthesis of 2-phenylthiazoline under various conditions[a]

Entry	[Bmim]Br_3 (mol%)	Temp. (°C)	Time (min)	Yield (%)[b]
1	0	100	60	0
2	0.1	100	30	56
3	0.2	100	20	68
4	0.3	100	20	75
5	0.5	100	10	86
6	0.5	110	5	90
7	1	25	60	46
8	1	80	20	69
9	1	90	10	89
10	1	100	5	96
11	1	110	5	95
12	1	120	5	95
13	1.5	100	5	96
14	2	100	5	94
15	2.5	100	5	93

[a]Reaction conditions: benzonitrile (1 mmol); 2-aminoethanethiol (1 mmol); neat.
[b]Isolated yield.

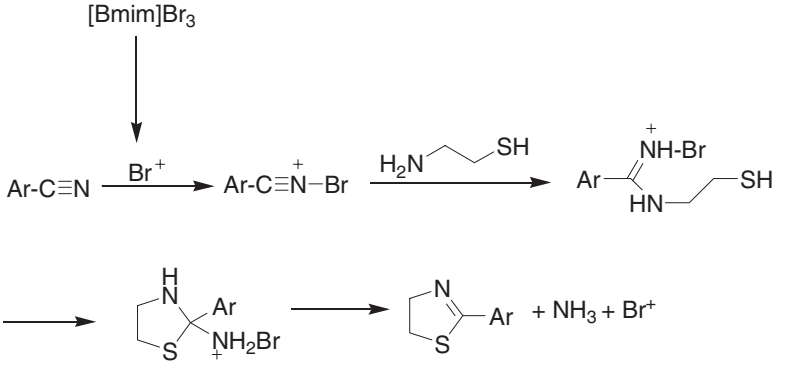
Table 2 Preparation of 2-arylthiazolines[a]

Entry	Ar	Time (min)	Products[b]	Yield (%)[b]	mp (lit.) (°C)
1	C_6H_5	5	**3a**	96	127–129 (126–128)[8c]
2	4-Cl-C_6H_4	4	**3b**	95	51–53 (53–55)[8e]
3	4-Me-C_6H_4	8	**3c**	85	40–41 (39–41[8e]
4	4-MeO-C_6H_4	8	**3d**	86	55–56 (53–55)[8c]
5	4-NO_2-C_6H_4	4	**3e**	92	147–149 (148–150)[8e]
6	4-F-C_6H_4	4	**3f**	94	Oil (oil)[8e]
7	3-NO_2-C_6H_4	6	**3g**	88	133–134 (135–137)[8c]
8	3-F-C_6H_4	6	**3h**	96	Oil
9	2-Pyridyl	10	**3i**	96	90–92 (91–93)[8e]
10	4-Pyridyl	8	**3j**	98	72–73 (74–76)[8e]

[a]Reaction conditions: nitrile (1 mmol); 2-aminoethanethiol (1 mmol); [Bmim]Br_3 (0.01 mmol); 100 °C; neat.
[b]Isolated yield.

2-substituted thiazolines (Table 2). As shown in Table 2, the direct reactions worked well with a variety of aryl nitriles including those bearing electron-withdrawing and electron-donating groups such as OMe, Cl, Br, and NO_2, and the desired compounds were obtained in good to excellent yields. Under the same conditions, this reaction did not proceed when aliphatic nitriles were used as the starting material.

Since [Bmim]Br_3 contains bromine atoms attached to nitrogen atoms, it is likely that it releases Br^+ in situ, which acts as a catalyst in the reaction medium. Therefore, the mechanism shown in Scheme 2 can be suggested for this conversion.



Scheme 2

CONCLUSION

We have described a simple, inexpensive, and efficient one-pot synthesis of 2-arylthiazoline derivatives under solvent-free conditions using a catalytic amount of [Bmim]Br_3 with excellent product yields. This method offers advantages such as mild reaction conditions, operational simplicity, and the use of economically viable reagents, which make it a useful and attractive process for the synthesis of 2-arylthiazolines.

EXPERIMENTAL

NMR spectra were measured on a Bruker AV-400 spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz) in $CDCl_3$ at r.t. using tetramethylsilane (TMS) as the internal standard; coupling constants (J) were measured in Hz. Elemental analyses were performed by a Vario-III elemental analyzer. Melting points were determined on a XT-4 binocular microscope and are uncorrected. [Bmim]Br_3 was prepared according to the literature.[13b] Commercially available reagents were used throughout without further purification unless otherwise stated.

General Procedure for the Synthesis of 2-arylthiazolines

A mixture of the nitrile (1 mmol), 2-aminoethanethiol (1 mmol), and [Bmim]Br_3 (0.01 mmol) was stirred at 100 °C for the appropriate time according to Table 2. After complete conversion as indicated by TLC, the reaction was cooled to r.t., and the crude product purified by column chromatography over silica gel using *n*-hexane/EtOAc (v:v = 2:1) as eluent to afford the pure product **3a–j**.

2-Phenylthiazoline (**3a**). IR (KBr) ν: 1572 (CN); ^{1}H NMR: δ 7.70 (d, 2H, J = 7.2 Hz, ArH), 7.44–7.37 (m, 3H, ArH), 4.42 (t, J = 8.0 Hz, 2H, CH_2N), 3.30 (t, J = 8.0 Hz, 2H, CH_2S); ^{13}C NMR: δ 165.2, 134.8, 130.9, 128.9, 128.4, 64.9, 33.8; Anal. calcd. for C_9H_9NS: C 66.22, H 5.56, N 8.58, S 19.64; found: C 66.30, H 5.52, N 8.62, S 19.62.

2-(4-Chlorophenyl)thiazoline (**3b**). IR (KBr) ν: 1576 (CN); ^{1}H NMR: δ 7.67 (d, 2H, J = 8.4 Hz, ArH), 7.32 (d, 2H, J = 8.4 Hz, ArH), 4.40 (t, J = 8.0 Hz, 2H, CH_2N), 3.32 (t, J = 8.0 Hz, 2H, CH_2S); ^{13}C NMR: δ 166.4, 138.2, 131.7, 129.9, 128.9, 64.5, 34.2; Anal. calcd. for C_9H_8ClNS: C 54.68, H 4.08, N 7.09, S 16.22; found: C 54.72, H 4.02, N 7.15, S 16.40.

2-(4-Methylphenyl)thiazoline (**3c**). IR (KBr) ν: 1565 (CN); ^{1}H NMR: δ 7.70 (d, 2H, J = 8.0 Hz, ArH), 7.26 (d, 2H, J = 8.0 Hz, ArH), 4.42 (t, J = 8.4 Hz, 2H, CH_2N), 3.36 (t, J = 8.4 Hz, 2H, CH_2S), 2.39 (s, 3H, CH_3); ^{13}C NMR: δ 167.9, 139.8, 131.2, 129.3, 128.6, 64.9, 34.1, 22.0; Anal. calcd. for $C_{10}H_{11}NS$: C 67.76, H 6.25, N 7.90, S 18.09; found: C 66.82, H 6.31, N 7.91, S 18.00.

2-(4-Methoxyphenyl)thiazoline (**3d**). IR (KBr) ν: 1574 (CN); ^{1}H NMR: δ 7.77 (d, 2H, J = 8.0 Hz, ArH), 6.98 (d, 2H, J = 8.0 Hz, ArH), 4.45 (t, J = 8.4 Hz, 2H, CH_2N), 3.85 (s, 3H, OMe), 3.39 (t, J = 8.4 Hz, 2H, CH_2S); ^{13}C NMR: δ 168.0, 159.8, 130.8, 126.9, 115.2, 65.2, 56.1, 34.2; Anal. calcd. for $C_{10}H_{11}NOS$: C 62.15, H 5.74, N 7.25, S 16.59; found: C 62.20, H 5.70, N 7.20, S 16.66.

2-(4-Nitrophenyl)thiazoline (**3e**). IR (KBr) ν: 1574 (CN); ^{1}H NMR: δ 8.31 (d, 2H, J = 8.8 Hz, ArH), 8.00 (d, 2H, J = 8.8 Hz, ArH), 4.50 (t, J = 8.4 Hz, 2H, CH_2N), 3.51 (t, J = 8.4 Hz, 2H, CH_2S); ^{13}C NMR: δ 165.2, 152.6, 143.0, 130.2, 124.3, 59.6, 33.4; Anal. calcd. for $C_9H_8N_2O_2S$: C 51.91, H 3.87, N 13.45, S 15.40; found: C 51.88, H 3.88, N 13.52, S 15.36.

2-(4-Fluorophenyl)thiazoline (**3f**). IR (KBr) ν: 1582 (CN); ^{1}H NMR: δ 7.82 (d, 2H, J = 8.4 Hz, ArH), 7.11 (d, 2H, J = 8.4 Hz, ArH), 4.43 (t, J = 8.4 Hz, 2H, CH_2N), 3.40 (t, J = 8.4 Hz, 2H, CH_2S); ^{13}C NMR: δ 165.9, 163.5, 130.6, 130.5, 130.0, 116.2, 115.7, 65.4, 34.3; Anal. calcd. for C_9H_8FNS: C 59.65, H 4.45, N 7.73, S 17.69; found: C 59.70, H 4.42, N 7.76, S 17.62.

2-(3-Nitrophenyl)thiazoline (**3g**). IR (KBr) ν: 1575 (CN); ^{1}H NMR: δ 8.68–8.22 (m, 3H, ArH), 7.66 (t, 1H, J = 8.0 Hz, ArH), 4.49 (t, J = 8.4 Hz, 2H, CH_2N), 3.50 (t, J = 8.4 Hz,

2H, CH_2S); ^{13}C NMR: δ 166.1, 150.1, 138.2, 135.9, 130.2, 125.9, 123.1, 63.2, 33.8; Anal. calcd. for $C_9H_8N_2O_2S$: C 51.91, H 3.87, N 13.45, S 15.40; found: C 51.85, H 3.90, N 13.50, S 15.34.

2-(3-Fluorophenyl)thiazoline (**3h**). IR (KBr) ν: 1600 (CN); ^1H NMR: δ 7.68–7.50 (m, 2H, Ar), 7.38 (d, 1H, $J = 7.6$ Hz. Ar), 7.22 (t, 1H, $J = 7.6$ Hz, Ar), 4.20 (t, $J = 8.0$ Hz, 2H, CH_2N), 3.32 (t, $J = 8.0$ Hz, 2H, CH_2S); ^{13}C NMR: δ 165.8,163.9, 138.3, 131.2, 125.2, 118.2, 113.9, 64.2, 33.9; Anal. calcd. for C_9H_8FNS: C 59.65, H 4.45, N 7.73, S 17.69; found: C 60.01, H 4.39, N 7.70, S 17.55.

2-(2-Pyridyl)thiazoline (**3i**). IR (KBr) ν: 1578 (CN); ^1H NMR: δ 8.56 (d, 1H, $J = 8.4$ Hz. ArH), 8.04 (d, 1H, $J = 8.4$ Hz, ArH), 7.69–7.30 (m, 2H, ArH), 4.46 (t, $J = 8.8$ Hz, 2H, CH_2N), 3.32 (t, $J = 8.8$ Hz, 2H, CH_2S); ^{13}C NMR: δ 166.9, 152.4, 152.0, 136.9, 132.6, 124.2, 63.6, 34.2; Anal. calcd for $C_8H_8N_2S$: C 58.51, H 4.91, N 17.06, S 19.52; found: C 58.60, H 4.99, N 17.01, S 19.55.

2-(4-Pyridyl)thiazoline (**3j**). IR (KBr) ν: 1582 (CN); ^1H NMR: δ 8.71 (dd, 2H, $J =$ 1.6, 4.8 Hz. ArH), 7.72 (dd, 2H, $J = 1.6$, 4.8 Hz, ArH), 4.49 (t, $J = 8.4$ Hz, 2H, CH_2N), 3.42 (t, $J = 8.8$ Hz, 2H, CH_2S); ^{13}C NMR: δ 167.2, 150.2, 144.3, 125.2, 62.8, 34.1; Anal. calcd. for $C_8H_8N_2S$: C 58.51, H 4.91, N 17.06, S 19.52; found: C 58.55, H 4.92, N 17.05, S 19.58.

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