1,3-Dibromo-5,5-dimethylhydantoin as an efficient homogeneous catalyst for the synthesis of 2-aryltiazolines and 2-arylimidazolines

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Abstract: A simple, facile, and efficient procedure for the synthesis of 2-aryltiazolines and 2-arylimidazolines has been developed by the simple condensation of nitriles with 2-aminoethanethiol or ethylenediamine catalyzed by 1,3-dibromo-5,5-dimethylhydantoin under solvent-free conditions. Selective preparation of bisthiazolines and monoimidazolines from dinitriles and also selective conversion of arylnitriles to their corresponding 2-aryltiazolines or imidazolines in the presence of alkylnitriles can be considered as considerable advantages of this method.

Key words: thiazoline, imidazoline, 1,3-dibromo-5,5-dimethylhydantoin, solvent-free

Introduction

Thiazolines and imidazolines are very important structural moieties, because they are found in a large number of biologically active natural products.1,2 The most significant examples are thiangazole,3 tantazole B,3 lissoclinamides,4 curacin A,5 naphazoline,6 xylometazoline,7 and oxymetazoline,8 which are anti HIV-1 and 2, antineoplastic and antimitotic agents, α-adrenergic agonists, nasal decongestants, and α-1 and α-2 agonist topical decongestants, respectively. Antidiabetic,9 antihypertensive,10 antihypercholesterolemic,11 and anti-inflammatory12 activities are some other properties which have been reported for the natural and synthetic thiazoline and imidazoline containing compounds.

Optically active mono- and bis-derivatives of these heterocycles have been efficiently used as both auxiliaries and ligands in asymmetric transformations.13 Furthermore, thiazoline derivatives have found industrial applications due to their ability to enhance the flavor and (or) aroma of various materials.14

Different methods have been developed for the synthesis of these biologically active heterocycles.15–21 Various precursors, catalysts, and reaction conditions have been applied for this purpose. Although some of these protocols efficiently generate the desired compounds, most of them suffer from one or more drawbacks such as long reaction times,16 harsh reaction conditions,17 low yields of products,18 use of expensive reagents17c,19 or toxic solvents,20 and using multistep syntheses.15e,18b,21 Therefore, the design of a new, simple, safe, and efficient method for the preparation of thiazolines and imidazolines is still challenging.

1,3-Dibromo-5,5-dimethylhydantoin (DBH) is a five-membered heterocycle, which had been known as a bromination agent,22 but it has recently gained special attention as an efficient homogeneous catalyst in organic transformations.23 However, we were interested in examining the catalytic activity of DBH on our previous work15d,24 on the synthesis of 2-aryltiazolines and 2-arylimidazolines derivatives (Scheme 1).

Scheme 1. Synthesis of 2-aryltiazolines and 2-arylimidazolines catalyzed by DBH.

Results and discussion

The catalytic synthesis of thiazolines and imidazolines from nitriles by DBH was studied. At first, cyclocondensa-
tion of benzonitrile with 2-aminoethanethiol was carried out in the presence of different amounts of DBH. The temperature and solvent effects were also investigated (Table 1). The best result was obtained with 1:1:1:0.01 molar ratios of benzonitrile/2-aminoethanethiol/DBH at 110 °C under solvent-free conditions. 2-Phenythiazolines was obtained in 95% yield after 7 min. To show the catalytic activity of DBH, when benzonitrile was reacted with 2-aminoethanethiol in the absence of catalyst under the same reaction conditions, only 15% yield was obtained after 7 min. Thus, DBH is an efficient homogeneous catalyst for the synthesis of 2-substituted thiazolines. Furthermore, the turnover number of the catalyst in the present reaction (TON = 95) exhibits the high catalytic activity of DBH in the synthesis of 2-thiazolines. The applicability of this method was investigated by the reaction of different nitriles with 2-aminoethanethiol in the presence of 1 mol% DBH. Results are summarized in Table 2 (entries 1–10). Nitrogen-containing analogues of thiazolines were also prepared satisfactorily by the current procedure (Table 2, entries 11–16). As shown in Table 2, both electron-donating and -withdrawing substituted nitriles reacted very well and produced corresponding 2-thiazolines and 2-imidazolines in good to excellent yields.

It is noteworthy that bisthiazolines and monoimidazolines were selectively generated by this method (Table 3). As illustrated in Table 3, reactions of 1,3- and 1,4-dicyanobenzene with 2-aminoethanethiol produced bisthiazolines in 97% and 85% yield, respectively, whereas the same substrates, when reacted with ethylenediamine, gave exclusively monoimidazolines in 96% and 95% yield, respectively. Bisimidazolines were not obtained even by increasing the reaction times to 10 h.

It is also important to note that alkyl nitriles did not react with 2-aminoethanethiol and ethylenediamine under the same reaction conditions. So, several competitive reactions were performed between aryl nitriles and alkyl nitriles (Scheme 2), which showed an interesting selectivity. Only 2-arylthiazolines and 2-arylimidazolines were obtained after appropriate times, and alkyl nitriles remained intact in the reaction mixture. Consequently, the present method is potentially applicable for the chemoselective conversion of aryl nitriles to their corresponding 2-arylthiazolines and 2-arylimidazolines in the presence of alkyl nitriles.

Although the actual mechanism of the reaction is unclear, a reasonable explanation due to the high catalytic activity of DBH and mechanistic operation of DBH in similar reactions is shown in Scheme 3. 1,3-Dibromo-5,5-dimethylhydantion produces the bromonium ion (Br+) and activates the nitrile group by the formation of nitrogen cation A. The reaction follows by nucleophilic attack of 2-aminoethanethiol or ethylenediamine on activated nitrile B to afford C and D which are both N-activated by Br+. Finally, the corresponding 2-thiazoline or 2-imidazoline is produced by releasing NH3 and bromonium ion, which returns to the catalytic cycle (Scheme 3).

In conclusion, we have demonstrated a mild and efficient protocol for the preparation of 2-arylthiazolines and 2-arylimidazolines using DBH as a homogeneous catalyst. Chemo-selectivity, short reaction times, easy work-up, and high yields of products are noteworthy advantages of this protocol. Furthermore, the use of an inexpensive, approximately non-toxic, commercially available, and highly efficient catalyst under solvent-free conditions makes the current method economically acceptable and industrially applicable. We have also proposed a plausible mechanism for the present reaction.

### Experimental

All materials are commercial reagent grade and were obtained from Merck or Fluka. 1H NMR spectra were recorded on a Bruker AVANCE 500 MHz or on a Bruker AW 80 MHz, and TMS was used as an internal standard in a 80 MHz spectrometer. Melting points were taken on a Stuart Scientific SMP2 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a PLATFORM 8379E in 70 eV.

### General procedure for the preparation of 2-thiazolines and 2-imidazolines

A mixture of nitrile (2 mmol), 2-aminoethanethiol (2.2 mmol) or ethylenediamine (8 mmol), and DBH (0.02 mmol) was refluxed (110 °C) under solvent-free conditions for the appropriate time according to Table 2. After completion of the reaction as indicated by TLC (2:1 n-hexane/EtOAc for thiazolines and 4:1 EtOAc/CH3OH for imidazolines), the mixture was cooled to room temperature and the pure product was isolated by column chromatography.

### General procedure for the synthesis of bisthiazolines and monoimidazolines

To a mixture of dinitrile (2 mmol) and 2-aminoethanethiol (5 mmol) or ethylenediamine (16 mmol) was added DBH (0.04 mmol) and the mixture stirred at 110 °C for the appropriate time according to Table 3. The progress of the reaction was monitored by TLC (2:1 n-hexane/EtOAc for thiazolines and 4:1 EtOAc/CH3OH for imidazolines). After completion of the reaction, the mixture was cooled to room temperature and the crude product purified via silica gel column chromatography.

### 2-Phenythiazoline (3a)

Solid; mp 126–128 °C. 1H NMR (CDCl3, 500 MHz) δ: 3.40 (t, J = 8.3 Hz, 2H, CH2–S), 4.46 (t, J = 8.3 Hz, 2H, CH2–N), 7.38–7.49 (m, 3H, ArH), 7.85 (dd, J = 1.6 and 8.3 Hz, 2H, ArH).

### Table 1. Investigation of temperature and solvent effects on the synthesis of 2-phenylthiazoline in the presence of DBH.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (a,b) (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>—</td>
<td>50</td>
<td>60</td>
<td>5</td>
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<tr>
<td>2</td>
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<td>80</td>
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<td>—</td>
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<td>95</td>
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<td>7</td>
<td>CH3Cl2</td>
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<td>75</td>
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<td>8</td>
<td>Acetone</td>
<td>110</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>n-Hexane</td>
<td>110</td>
<td>7</td>
<td>30</td>
</tr>
</tbody>
</table>

(a) Reaction conditions: benzonitrile (1 mmol), 2-aminoethanethiol (1.1 mmol), and DBH (0.01 mmol).  
(b) Isolated yields.
Table 2. Synthesis of 2-thiazolines and 2-imidazolines catalyzed by DBH.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile (1)</th>
<th>Product (3)</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Mp (°C), Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td>7 min</td>
<td>95</td>
<td>126-128, 15a</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="" /></td>
<td><img src="image4" alt="" /></td>
<td>3 min</td>
<td>90</td>
<td>53-55, 15b</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="" /></td>
<td><img src="image6" alt="" /></td>
<td>9 min</td>
<td>83</td>
<td>Oil, 15c</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="" /></td>
<td><img src="image8" alt="" /></td>
<td>3 min</td>
<td>94</td>
<td>Oil, 15c</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="" /></td>
<td><img src="image10" alt="" /></td>
<td>8 min</td>
<td>82</td>
<td>151-153, 15b</td>
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<td>6</td>
<td><img src="image11" alt="" /></td>
<td><img src="image12" alt="" /></td>
<td>3 min</td>
<td>90</td>
<td>176-178, 15d</td>
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<tr>
<td>7</td>
<td><img src="image13" alt="" /></td>
<td><img src="image14" alt="" /></td>
<td>9 min</td>
<td>60</td>
<td>52-54, 15b</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="" /></td>
<td><img src="image16" alt="" /></td>
<td>8 min</td>
<td>95</td>
<td>92-94, 15e</td>
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<td><img src="image17" alt="" /></td>
<td><img src="image18" alt="" /></td>
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<td>110-112, 15f</td>
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<td><img src="image20" alt="" /></td>
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<td>96</td>
<td>74-76, 15d</td>
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<td><img src="image22" alt="" /></td>
<td>4 h</td>
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<td>100-102, 15g</td>
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<tr>
<td>12</td>
<td><img src="image23" alt="" /></td>
<td><img src="image24" alt="" /></td>
<td>2 h</td>
<td>88</td>
<td>134-136, 15h</td>
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<tr>
<td>13</td>
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<td><img src="image26" alt="" /></td>
<td>4 h</td>
<td>70</td>
<td>186-188, 15g</td>
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<td><img src="image27" alt="" /></td>
<td><img src="image28" alt="" /></td>
<td>0.5 h</td>
<td>97</td>
<td>100-102, 15h</td>
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<td><img src="image30" alt="" /></td>
<td>2 h</td>
<td>65</td>
<td>106-108, 15i</td>
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<td>16</td>
<td><img src="image31" alt="" /></td>
<td><img src="image32" alt="" /></td>
<td>2 h</td>
<td>90</td>
<td>134-136, 15i</td>
</tr>
</tbody>
</table>

*Products were identified by comparison of their physical and spectral data with those reported in the literature.

*Isolated yields.
**Scheme 2.** Competitive reactions of aryl and alkyl nitriles with 2-aminoethanethiol or ethylenediamine.

\[
\text{N}^\text{CN} + \text{Ph}-\text{CH}:\text{CHCN} + \text{H}_2\text{N} \rightarrow \text{N}^\text{+} + \text{Ph}-\text{CH}:\text{CHCN} + \text{H}_2\text{N} \rightarrow \text{N}^\text{+} + \text{Ph}-\text{CH}:\text{CHCN} + \text{H}_2\text{N}
\]


**Scheme 3.** Proposed mechanism for the synthesis of 2-arylthiazolines and 2-arylimidazolines catalyzed by DBH.

2-(4-Chlorophenyl)thiazoline (3b)

Solid; mp 53–55 °C. ¹H NMR (CDCl₃, 500 MHz) δ: 3.45 (t, \( J = 8.4 \), 2H, CH₂–S), 4.47 (t, \( J = 8.4 \) Hz, 2H, CH₂–N),
Table 3. Selective synthesis of bis-thiazolines and mono-imidazolines using DBH.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Product</th>
<th>Time</th>
<th>Yielda,b (%)</th>
<th>Mp (°C), Ref.</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image2.png" alt="image" /></td>
<td>9 min</td>
<td>97</td>
<td>111-113, 15d</td>
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<tr>
<td>2</td>
<td><img src="image3.png" alt="image" /></td>
<td><img src="image4.png" alt="image" /></td>
<td>14 min</td>
<td>85</td>
<td>105-107, 15b</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="image" /></td>
<td><img src="image6.png" alt="image" /></td>
<td>2.5 h</td>
<td>96</td>
<td>133-134, 15d</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="image" /></td>
<td><img src="image8.png" alt="image" /></td>
<td>3 h</td>
<td>95</td>
<td>207-209, 15j</td>
</tr>
</tbody>
</table>

aProducts were identified by comparison of their physical and spectral data with those reported in the literature.
bIsolated yields.

7.40 (d, J = 8.6 Hz, 2H, ArH), 7.79 (d, J = 8.6 Hz, 2H, ArH). MS m/z: 197, 199 [M⁺]. Anal. calcd for C₉H₈ClNS: C 54.68, H 4.08, N 7.08; found C 54.53, H 4.17, N 7.09.

2-(3-Bromophenyl)thiazoline (3c)

Oily Liquid. ¹H NMR (CDCl₃, 500 MHz) δ: 3.36 (t, J = 8.1 Hz, 2H, CH₂–S), 4.26 (t, J = 8.1 Hz, 2H, CH₂–N), 7.27 (t, J = 7.8 Hz, 1H, ArH), 7.40 (d, J = 7.9 Hz, 1H, ArH), 7.50 (d, J = 7.6 Hz, 1H, ArH), 7.66 (s, 1H, ArH). MS m/z: 241, 243 [M⁺]. Anal. calcd for C₉H₈BrNS: C 44.64, H 3.33, N 5.78; found C 44.67, H 3.37, N 5.72.

2-(4-Bromophenyl)thiazoline (3d)

Oily liquid. ¹H NMR (CDCl₃, 500 MHz) δ: 3.35 (t, J = 8.1 Hz, 2H, CH₂–S), 4.24 (t, J = 8.2 Hz, 2H, CH₂–N), 7.31 (d, J = 8.2 Hz, ArH), 7.55 (d, J = 8.2 Hz, 2H, ArH). MS m/z: 241, 243 [M⁺]. Anal. calcd for C₉H₈BrNS: C 44.64, H 3.33, N 5.78; found C 44.67, H 3.37, N 5.72.

2-(4-Nitrophenyl)thiazoline (3e)

Solid; mp 151–153 °C. ¹H NMR (CDCl₃, 500 MHz) δ: 3.53 (t, J = 8.5 Hz, 2H, CH₂–S), 4.54 (t, J = 8.5 Hz, 2H, CH₂–N), 8.02 (d, J = 8.8 Hz, 2H, ArH), 8.29 (d, J = 8.7 Hz, 2H, ArH). MS m/z: 215 [M⁺]. Anal. calcd for C₉H₈N₂O₂S: C 51.91, H 3.87, N 13.45; found C 51.88, H 3.80, N 13.52.

2-(4-Hydroxyphenyl)thiazoline (3f)

Solid; mp 52–54 °C. ¹H NMR (CDCl₃, 500 MHz) δ: 3.42 (t, J = 8.2 Hz, 2H, CH₂–S), 3.86 (s, 3H, O–CH₃), 4.44 (t, J = 8.2 Hz, CH₂–N), 6.93 (d, J = 8.3 Hz, 2H, ArH), 7.81 (d, J = 8.3 Hz, 2H, ArH). MS m/z: 197 [M⁺]. Anal. calcd for C₉H₉NOS: C 60.31, H 5.06, N 7.81; found C 60.43, H 5.00, N 7.78.

2-Phenylimidazoline (3k)

Solid; mp 100–102 °C. ¹H NMR (CDCl₃, 500 MHz) δ: 3.75 (s, 4H, 2CH₂), 4.8 (s, 1H, NH), 7.3–7.4 (m, 3H, ArH), 7.7–7.8 (m, 2H, ArH). MS m/z: 146 [M⁺]. Anal. calcd for C₁₀H₁₃N₂: C 73.94, H 6.89, N 19.16; found C 73.95, H 6.85, N 19.18.

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2-(3-Chlorophenyl)imidazoline (3I)
Solid; mp 134–136 °C. \(^1^H\) NMR (CDCl\(_3\), 80 MHz): \(\delta\): 3.76 (s, 4H, 2CH\(_2\)), 4.25 (s, 1H, NH), 7.22–7.75 (m, 4H, ArH). MS \(m/z\): 180, 182 \([M^+]\). Anal. calcd. for C\(_{10}\)H\(_9\)N\(_3\): C 70.16, H 5.30, N 24.54; found C 70.15, H 5.33, N 24.52.

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References

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