Efficient 2,4,6-Trichloro-1,3,5-triazine-Catalyzed Synthesis of 2-Arylbenzothiazoles and Bisbenzothiazoles by Condensation of 2-Aminothiophenol with Aldehydes under Mild Conditions

Behrooz Maleki,*a Davood Azarifar,b Seyede Fateme Hojati,a Hojat Veisi,a Mostafa Gholizadeh,d Hafezeh Salehabadi,a and Mona Khodaverdian Moghadama

aDepartment of Chemistry, Sabzevar Tarbiat Moallem University, Sabzevar, Iran
bDepartment of Chemistry, Bu-Ali Sina University, Hamadan, Iran
cDepartment of Chemistry, Payame Noor University, Songhor, Kermanshah, Iran
dDepartment of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran

*E-mail: maleki@sttu.ac.ir

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2,4,6-Trichloro-1,3,5-triazine efficiently catalyzed the condensation reactions between 2-aminothiophenol and aromatic aldehydes to afford 2-arylbenzothiazoles in good-to-excellent yields. Simple and mild reaction conditions, the use of a cheap catalyst and easy work up, and isolation are notable features of this method.


INTRODUCTION

2-Arylbenzothiazoles have been investigated extensively by organic chemists due to their medicinal properties such as antitumor [1], antiviral, and antimicrobial drugs [2]. Also, some benzothiazoles have been found in some organisms [3]. Therefore, there is interest in developing methods for their synthesis.

Numerous methods are available for the synthesis of 2-arylbenzothiazoles and the important ones include the reaction of o-aminothiophenols with carboxylic acids [4], the potassium ferricyanide cyclization of thiocyanates or benzaldehydes (Jacobson’s method) [5], the palladium-catalyzed reaction of aryl halides with o-aminothiophenol in the presence of carbon monoxide [6], the ceric ammonium nitrate mediated reaction of thiophenols with aromatic nitriles [7], and flash vacuum pyrolysis and photolysis of 2-methylthio-N-(arenylidene)aniline [8].

On the other hand, the most general synthetic approaches for synthesis of 2-arylbenzothiazoles involve condensation of 2-aminothiophenols with aldehydes using various oxidants such as MnO2/SiO2 [9], p-TsOH or graphite on the surface of solid mineral supports under microwave irradiation [10], I2/DMF [11], 1-phenyl-3-methylimidazolium bromide by microwave irradiation [12], activated carbon (Shirasagi KL or Darco® KB) under oxygen atmosphere [13], O2 or H2O2 in the presence of Sc(OTf)3 [14], tungstophosphoric acid impregnates zirconium phosphate [15], electrooxidation [16], Dowex 50W [17], and direct condensation of 2-aminothiophenol with aromatic aldehydes under microwave irradiation [18].

RESULTS AND DISCUSSION

In development of benzothiazoles synthetic methodologies [19] and as a part of our research interest toward the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions [20], we report here a facile synthesis of 2-arylbenzothiazoles in the presence of oxygen and a catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) at room temperature (Scheme 1).

In recent years, 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) has been used in organic synthesis because it is stable, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent [21].

In the initial exploratory experiments, we optimized the reaction condition by testing several parameters, such as different amounts of TCT and different solvents. As a test case, the reaction of 2-aminothiophenol (1.2 mmol) with benzaldehyde (1 mmol) was carried out in the presence of TCT in CH3CN to afford the 2-phenylbenzothiazoles (2a).

In the experiments carried out to establish the optimal amount of TCT, the reaction with a 3 mol % catalyst loading gave 87% yield after 3 h. Increasing the amount of the catalyst (5, 7, and 10 mol %) did not
change the isolated yield and the time reaction (3 h). The solvent effect in this reaction was also studied, and it was found that CH$_3$CN gave the best results among H$_2$O, MeOH, CHCl$_3$, CH$_2$Cl$_2$, and EtOH solvents. Similarly, by adopting optimized reaction conditions, the various 2-arylbenzothiazoles were prepared by condensation of 2-aminothiophenol with aromatic aldehydes (1a–l) in presence of 3 mol% TCT in CH$_3$CN (Table 1).

The present conversion did not precede under perfectly anhydrous reaction conditions. The proposed mechanism for the TCT-catalyzed synthesis of 2-arylbenzothiazoles may tentatively be visualized to occur via a tandem sequence of reactions as depicted in

![Scheme 1](image)

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde (1a–l)</th>
<th>2-Arylbenzothiazole (2a–l)</th>
<th>Time (h)</th>
<th>Yield (%) $^a$</th>
<th>Observed mp (°C)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>3</td>
<td>87</td>
<td>111–112</td>
<td>112–114 [17]</td>
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<tr>
<td>2</td>
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<td></td>
<td>3</td>
<td>84</td>
<td>103–105</td>
<td>101–103 [17]</td>
</tr>
<tr>
<td>3</td>
<td>MeO-</td>
<td></td>
<td>2.5</td>
<td>80</td>
<td>119–120</td>
<td>120–121 [17]</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td></td>
<td>3.5</td>
<td>84</td>
<td>127–128</td>
<td>127–128 [22a]</td>
</tr>
<tr>
<td>5</td>
<td>OH</td>
<td></td>
<td>4</td>
<td>78</td>
<td>82–84</td>
<td>85 [22a]</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td></td>
<td>4.5</td>
<td>80</td>
<td>52–54</td>
<td>53–54 [22a]</td>
</tr>
<tr>
<td>7</td>
<td>CHO</td>
<td></td>
<td>2.5</td>
<td>86</td>
<td>132–133</td>
<td>132 [17]</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td></td>
<td>3</td>
<td>84</td>
<td>82–83</td>
<td>83–84 [17]</td>
</tr>
<tr>
<td>9</td>
<td>(CH$_3$)$_2$N-</td>
<td></td>
<td>30$^b$</td>
<td>80</td>
<td>157–159</td>
<td>160–161 [17]</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td></td>
<td>2.5</td>
<td>80</td>
<td>116–118</td>
<td>115–117 [17]</td>
</tr>
<tr>
<td>11</td>
<td>CN</td>
<td></td>
<td>2</td>
<td>90</td>
<td>161–162</td>
<td>162–164 [10]</td>
</tr>
<tr>
<td>12</td>
<td>NO$_2$</td>
<td></td>
<td>3</td>
<td>86</td>
<td>179–180</td>
<td>181–182 [17]</td>
</tr>
</tbody>
</table>

$^a$ The yields refer to those of isolated products characterized by spectroscopic (IR, $^1$H, $^1$C-NMR) data.

$^b$ Reaction time is min.
(Scheme 2) involving TCT [20e], which reacts with “incipient” moisture and releases 3 mol of HCl and cyanuric acid (removable by washing with water) as a by-product. The in situ generated HCl acts as a protic acid and activates the carbonyl oxygen to promote the condensation of 2-aminothiophenol with aldehydes to form adduct [A], which then undergoes cyclization to give adduct [B], followed by oxidation with oxygen (air) to form 2-arylbenzothiazoles (2a–l).

On the basis of previously reported mechanism for the synthesis of 2-arylbenzothiazoles in the presence of various catalytic amounts [9,13,17,18,20a,21a], and because of our observation in during the synthesis of 2-arylbenzothiazoles using TCT, we assume that HCl is generated from TCT as the active catalyst in the reaction medium. To confirm our assumption, we replaced the TCT by 10 mol % of HCl. A test reaction was performed between 4-chlorobenzaldehyde (1 mmol) and 2-aminothiophenol (1.2 mmol) in the presence of HCl (10 mol %) at 70°C without solvent. It was found that the generation of 2-(4-chlorophenyl) benzothiazole occurred in 54% after 5 h. To show the accessibility of the present work in comparison with the reported results with TCT, we summarized some of the results for the preparation of 2-arylbenzothiazoles using HCl in Table 2.

It is important to mention that, when the reaction of 2-chlorobenzaldehyde (1 mmol) and 2-aminothiophenol (1.2 mmol) was carried out in the presence of TCT (3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>2-Arylbenzothiazole</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Observed mp (°C)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl-C≡CH</td>
<td>5b</td>
<td>54</td>
<td>15–116</td>
<td>115–117 [17]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Br-C=CH</td>
<td>20c</td>
<td>52</td>
<td>84–86</td>
<td>83–84 [17]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeO-C≡C</td>
<td>15c</td>
<td>48</td>
<td>120–121</td>
<td>120–121 [17]</td>
<td></td>
</tr>
</tbody>
</table>

a The yields refer to those of isolated products characterized by spectroscopic (IR, 1H, 13C-NMR) data.
b Reaction carried out under solvent-free condition at 70°C.
c Reaction carried out in EtOH at room temperature.
mol %) under nitrogen atmosphere (in the absence of oxygen), the reactions stopped at the 2-(2-chlorophenyl)benzothiazoline (mp 75–77°C, lit. 76°C [17]) stage, which never proceeded to benzothiazoles. The isolated 2-(2-chlorophenyl)benzothiazoline (1 mmol) reacted with TCT (3 mol %) in the presence of O₂ (air) to afford the corresponding 2-(2-chlorophenyl)benzothiazole (mp 82–83°C, lit. 81–83°C [10]). This surely proves that aerial oxygen is not essential for 2-arylbenzothiazoline (B) formation, though it is absolutely essential for the oxidation step leading to the formation of 2-arylbenzothiazoles (Scheme 3).

Having successfully performed the reactions of 2-aminothiophenol with a wide range of aldehydes, we focused our attention on examining the reaction of 2-aminothiophenol with 1,4-benzenedicarbaldehydes to TCT in CH₃CN at room temperature (Scheme 4).

Finally, we have developed this synthetic method for the preparation of additional extended bisbenzothiazole derivatives in a 2:1 molar ratio of 2-aminothiophenol to 1,4-benzenedicarbaldehyde with 10 mol % TCT in CH₃CN. The reaction proceeded smoothly for 3 h at room temperature using the present protocol, and the desired product 2m was obtained in 94% isolated yield, mp 258–260°C (lit. 258°C) [23].

In conclusion, we developed a new application for 2,4,6-trichloro-1,3,5-triazine. By using this catalyst, a series of 2-arylbenzothiazoles and bisbenzothiazoles were obtained in high yields via condensation of 2-aminothiophenol with aldehydes under mild condition. Simple workup and easy isolation under mild reaction conditions are the best features of the present methodology.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KB). ¹H-NMR spectra were obtained using JEOL FT NMR 90 MHz spectrometer in CDCl₃ using TMS as an internal reference. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected.

Typical experimental procedure for the synthesis of 2-arylbenzothiazoles by condensation 2-aminothiophenol with aldehydes using 2,4,6-trichloro-1,3,5-triazine. To a stirred solution of 2-aminothiophenol (1.2 mmol) in CH₃CN (5 mL), an aldehyde (1a–l, 1 mmol) and 3 mol % TCT were added. The reaction mixture was stirred at room temperature until the reaction was complete, as judged by TLC (eluent: hexane-EtOAc = 5:1) analysis. After completion, the solvent was evaporated and the residue was washed with water to give the crude products (2a–l). The residue was then recrystallized from (EtOH, 5 mL) to afford the pure product.

Selected physical and spectroscopic data of isolated the products. 2-Phenylbenzothiazole (2a). Mp 111–112°C (lit. 112–114°C [17]); ¹H-NMR (90 MHz, CDCl₃): δ 7.41–8.08 (m, H Ar); ¹³C-NMR (22.5 MHz, CDCl₃): δ 77.10 (CDCl₃), 121.53, 123.23, 125.09, 126.22, 127.52, 128.91, 130.83, 133.64, 135.08, 154.19, 167.93; IR (KBr): 3064, 1588, 1555, 1509, 1478, 1433, 1244, 962, 766 cm⁻¹.

2-(4-Methoxyphenyl)benzothiazole (2c). Mp 119–120°C (lit. 120–121°C [17]); ¹H-NMR (90 MHz, CDCl₃): δ 3.82 (s, 3H, OMe), 7.00–7.95 (m, 8H, H Ar); ¹³C-NMR (22.5 MHz, CDCl₃): δ 77.10 (CDCl₃), 55.45 (OCH₃), 114.34, 121.53, 122.90, 124.81, 126.21, 129.16, 134.91, 154.38, 162.02, 167.85; IR (KBr): 3023, 2996, 2936, 2836, 1605, 1521, 1485, 1434, 1384, 1312, 760 cm⁻¹.

2-(4-Methylphenyl)benzothiazole (2e). Mp 84–86°C (lit. 85°C [22a]); ¹H-NMR (90 MHz, CDCl₃): δ 2.38 (s, 3H, CH₃), 7.30–8.01 (m, 8H, H Ar); IR (KBr): 3024, 2996, 2900, 2836, 1605, 1521, 1485, 1260, 832 cm⁻¹.

2-(4-Cyanophenyl)benzothiazole (2k). Mp 161–162°C (lit. 162–164°C [10]); ¹H-NMR (90 MHz, CDCl₃): δ 7.37–7.96 (m, H Ar); ¹³C-NMR (22.5 MHz, CDCl₃): δ 77.10 (CDCl₃), 113.93, 118.08, 121.66, 123.68, 125.96, 126.69, 127.68, 132.50, 137.20, 138.18, 165.09; IR (KBr): 3058, 1611, 1576, 1529, 1459, 1433, 1437, 761 cm⁻¹.

2-(3-Nitrophenyl)benzothiazoles (2l). Mp 179–180°C (lit. 181–182°C [17]); ¹H-NMR (90 MHz, CDCl₃): δ 7.44–8.30 (m, 7H, H Ar); IR (KBr): 3058, 1611, 1576, 1529, 1459, 1433, 1347, 761 cm⁻¹.
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REFERENCES AND NOTES