An Efficient Acid- and Metal-Free One-Pot Synthesis of Benzothiazoles from Carboxylic Acids

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Abstract: Carboxylic acids are converted to benzothiazoles in a one-pot reaction with thionyl chloride followed by treatment with 2-aminothiophenol under acid- and catalyst-free conditions.

Key words: benzothiazoles, carboxylic acids, thionyl chloride, 2-aminothiophenol, acid-free, catalyst-free

Benzothiazoles constitute an important class of compounds with profound interest to medicinal/industrial chemists, as compounds bearing the benzothiazolyl moiety exhibit diverse biological properties such as antitumour,1 antimicrobial,2 antigliutamate/antiparkinsonian3, broad spectrum Ca2+ channel antagonist,4 inhibition of enzymes such as aldose reductase,5 monoamine oxidase,6 lipoxigenase,7 cyclooxygenase,8 acetylcholine esterase,9 thrombine,10 proteases,11 H+-K+ ATPase,12 carbonic anhydrase,13 HCV helicase,14 plant growth regulation,15 and have industrial applications as antioxidants16 and vulcanization accelerators.17

The methodologies developed following the strategy A (Scheme 1) involve the reaction of 2-aminothiophenol (1) with carboxylic acids in the presence of polyphosphoric acid14,18 or P2O5-MeSO3H,19 selenoesters,20 selenoamides,21 aldehydes under microwave irradiation catalyzed by silica or montmorillonite clay,22 and esters under heating at 160 °C23 or reflux in toluene in the presence of base-promoted intramolecular nucleophilic aromatic substitution of o-halothiobenzanilides in NMP or DMF24 and demethylative cyclization of o-(methylthio)anilides with phosphonitrilic dichloride.25 Other methods are reaction of copper(I) thiobenzoate with 2-iodoaniline in HMPT,26 treatment of 1 with haloaromatics involving palladium-catalyzed carbylation under high pressure,27 p-TsOH-catalyzed degradative cyclization of 1 with β-chlorocinnamaldehyde derivatives under microwave irradiation,28 and palladium-catalyzed Suzuki coupling reaction of 2-bromobenzothiazoles with arylboronic acids.29 These methodologies suffer from one or more of the disadvantages such as the lack of ease of availability/preparation of the starting material, prolonged reaction time (four hours to four days), use of costly, air sensitive, and toxic substances, requirement of excess of reagents/catalysts, and harsh reaction conditions. The products obtained under metal-catalyzed conditions are frequently contaminated with trace amount of metals, due to strong coordinating property of thiazole moiety and pose problem in biological testing. Thus, these disadvantages necessitate the development of alternate synthetic route.

We felt that, a direct conversion of carboxylic acids to benzothiazoles (strategy A, Scheme 1) under acid- and catalyst-free conditions should be the method of choice. However, the poor leaving group property of the OH– anion does not make the condensation feasible. Thus, we recently developed a new method by direct condensation of carboxylic acids with 1 under microwave irradiation.30 The reaction worked less well with aromatic carboxylic acids due to the loss of the carboxylic acid through sublimation and decarboxylation. In an alternate strategy, the hydroxyl group of the carboxylic acid was converted to phenolate moiety to serve as a better leaving group.30 However, the use of 1-methyl-2-pyrrolidone (NMP) as solvent and the additional synthetic step required to form the aryl esters do not fulfill the projected objectives. The use of acid chloride increases the electrophilicity of the carbonyl carbon but one feels the necessity to use a base either to increase the nucleophilicity of the thiophenolate moiety or to scavenge the liberated HCl.31 Brembilla et al.32 used NMP as solvent that served as scavenger for the liberated HCl. However, the method was limited to the commercial availability of the acid chloride and did not include substrates having α hydrogens that are susceptible to undergo competitive ketene formation. Furthermore, the high boiling point and miscibility in water of NMP make the solvent recovery difficult and the process becomes unattractive both on economic and environmental aspects. The use of disopropylethylamine as proton scavenger was associated with the formation of azoxybenzen derivative as the byproduct during the reaction of 1 with acid chlorides in DMF.36
We thought that in situ generation of the acid chloride should solve the problem of commercial availability of acid chlorides and the use of a nonpolar reaction medium circumvent the problem of competitive side reaction of acid chlorides bearing α hydrogens and provide a cost effective synthesis. Additionally, the liberated HCl should activate the intermediate thioacylated derivative for nucleophilic attack by the ortho-amino group and make the cyclization facile and effective under mild condition.

To test this hypothesis, commercially available phenylacetyl chloride (2, 1 equiv) was treated with 1 (1 equiv) at room temperature under solvent-free conditions. We were delighted to observe that 2-benzylbenzothiazole (3) was obtained in 90% yield in one hour. In trying to establish the reproducibility, we noticed a wide variation (50–90%) in product yields from batch to batch experiments and bis-(2-aminophenyl)disulfide was obtained as byproduct in those cases where the yields of 3 were less. We thought that the batchwise variation may be due to the trapping of the unreacted acid chloride by the precipitated solid product (the intermediate thioacylated derivative and the benzothiazole) and the use of a suitable solvent should circumvent this problem. Therefore, 2 was treated with 1 in various solvents at room temperature (Table 1).

The best results were obtained in nonpolar solvent such as toluene affording 3 in consistent yields (92–100%) on repeated attempts (Table 1). Reasonable yields were obtained in weakly polar solvents such as (CH₂)₄O, (CH₂CH₂)₂O₂, (CH₂)₂Cl₂ and MeCN (entries 2–5). However, inferior results were obtained with aprotic polar solvents such as MeNO₂ and NMP (entries 6–8). The better results obtained in weakly polar solvents (entries 2–5) justified the role of in situ liberated HCl in catalyzing the condensation in final step. Although NMP has been used as a solvent during the reaction of acid chloride with 1, we observed the formation of a complex mixture containing the expected product in NMP at room temperature (entry 7) and at 100 °C (entry 8) after 1 hour. We presumed that in NMP, the naked Cl⁻, generated from the liberated HCl, acts as base for proton abstraction form acid chloride having α hydrogens and makes the methodology unsuitable for aliphatic acid chlorides. Thus, various acid chlorides were treated with 1 in toluene and excellent results were obtained in most of the cases (Table 2).

Since many acid chlorides are not commercially available, we planned to synthesize benzothiazoles from carboxylic acids in a one-pot reaction by in situ preparation of the acid chloride. In a separate experiment, phenylacetic acid (1 equiv) was treated with thionyl chloride (1.2 equiv) under neat condition at 80 °C for one hour followed by 2- aminothiophenol (1, 1 equiv) in toluene at room temperature for one hour resulting in the formation of 3 in 98% yield. To establish the generality, various carboxylic acids were subjected to benzothiazole formation following the one-pot reaction (Table 3).

Table 1: Effect of Solvent on Benzothiazole Formation from the Reaction of 1 with 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(CH₂)₄O</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(CH₂CH₂)₂O₂</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(CH₂)₂Cl₂</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MeNO₂</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>NMP</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NMP</td>
<td>53c</td>
<td></td>
</tr>
</tbody>
</table>

a Compound 2 (2.5 mmol) was treated with 1 (2.5 mmol) in the solvent (2.5 mL) at r.t. (except entry 8) for 1 h.
b HPLC yield of 3.
c The reaction was carried out at 100 °C.

Table 2: Synthesis of Benzothiazoles by the Reaction of 1 with Various Acid Chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Chloride</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃COCl</td>
<td>0.25</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CH₂CH₂COCl</td>
<td>0.5</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>t-BuCOCl</td>
<td>0.25</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂COCl</td>
<td>0.25</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PhCOCl</td>
<td>0.25</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(E)-PhCH=CHCOCl</td>
<td>1</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

a The acid chloride (2.5 mmol) was treated with 1 (2.5 mmol) in toluene (2.5 mL) at r.t.
b Isolated yield of the corresponding benzothiazole.

c One example for each entry is shown.

Table 3: One-Pot Synthesis of Benzothiazoles from Various Carboxylic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic Acid</th>
<th>Yield (%)</th>
<th>b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = H, n = 1</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R = 4-OMe; n = 1</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R = H, n = 2</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R = H, n = 3</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R¹ = R² = R³ = R⁴ = H</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R¹ = R² = R³ = H, R⁴ = OMe</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>
The reactions were carried out in two stages. Initially, the carboxylic acid was treated with thionyl chloride (1.2 equiv) under neat conditions at 80 °C till complete consumption of the carboxylic acid (1–3 h). The progress of the acid chloride formation was monitored by quenching an aliquot portion of the reaction mixture with a few drops of MeOH followed by TLC. The disappearance of the starting carboxylic acid and formation of a new spot (methyl ester) revealed completion of acid chloride formation. A direct monitoring was not feasible due to the trailing effect of the acid chloride on the TLC plate. In the second stage, excess thionyl chloride was distilled off and the acid chloride treated with 2-aminothiophenol in toluene at room temperature for one hour. We observed an exothermic reaction during the addition of to the acid chloride. Therefore, the mixing of the acid chloride and was carried out at 0–5 °C. Excellent results were obtained in most of the cases (Table 3). The reaction worked well for aromatic (entries 5–8, 11–15, 24, and 25), heteroaromatic (entries 21–23), and arylalkyl (entries 1–4, 16–18 and 26) and aliphatic carboxylic acids (entry 27). Excellent chemoselectivity was observed for substrates susceptible to undergo nucleophilic substitution reactions, Michael addition, and reduction as the sulphydryl moiety is a good nucleophile and thiols are capable to function as single electron-transfer agents. No aromatic nucleophilic substitution of the chloro/nitro (entries 7, 8, and 17) and reduction of the nitro group (entry 8) took place. No nucleophilic substitution of the phenoxide moiety was observed during the reaction with phenoxy, 4-chlorophenoxy, and thiophenoxy acetic acids (entries 16–18). Although thiols are commonly used for aryl methyl ether cleavage, no competitive demethylation was observed for substrates containing aryl methyl ether functionality (entries 2, 6, 11–14, and 20). Cinnamic acid (entry 19) and 4-methoxycinnamic acid (entry 20) afforded the desired benzothiazole derivative without any competitive Michael addition or reduction of the double bond. However, the presence of an amino or hydroxyl group in the carboxylic acid was found to be detrimental for the formation of the desired product. No significant benzothiazole formation took place with 4-hydroxy- and 4-aminobenzoic acids (entries 9 and 10). The TLC of the aliquot portion of the reaction mixture after quenching with MeOH did not reveal the formation of the corresponding methyl esters. It is anticipated that self condensation involving the acyl chloride and the hydroxyl/aminogroups leads to the side product formation. The reaction of 3,5-dimethoxy-4-hydroxybenzoic acid afforded a 52% yield (entry 14). 2-Hydroxynaphthalene and 1-hydroxynaphthalene were identified (GC-MS) as the major products during the reactions with 2-hydroxy-1-naphthoic acid and 1-hydroxy-2-naphthoic acid, respectively, presumably due to decarboxylation. The reactions with dicarboxylic acids such as phthalic acid (entry 15) and succinic acid (entry 27) led to the formation of the corresponding monobenzothiazoles. In general, the product obtained after the usual work-up was of sufficient purity (GC-MS) and did not require further pu-

### Table 3 One-Pot Synthesis of Benzothiazoles from Various Carboxylic Acids (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic Acid</th>
<th>Yield (%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H, R&lt;sup&gt;3&lt;/sup&gt; = Cl</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H, R&lt;sup&gt;3&lt;/sup&gt; = NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H, R&lt;sup&gt;3&lt;/sup&gt; = NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H, R&lt;sup&gt;3&lt;/sup&gt; = OH</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = OMe, R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = OMe</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = OMe</td>
<td>72</td>
</tr>
<tr>
<td>14</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = OMe, R&lt;sup&gt;3&lt;/sup&gt; = OH</td>
<td>52</td>
</tr>
<tr>
<td>15</td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = CO&lt;sub&gt;2&lt;/sub&gt;H, R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = H</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The carboxylic acid (1 equiv) was treated with thionyl chloride (1.2 equiv) at 80 °C for 1 h followed by addition of I (1 equiv) at r.t. in toluene for 1 h.

<sup>b</sup>Isolated yield of the corresponding 2-substituted benzothiazole.

<sup>c</sup>All compounds were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS.

<sup>d</sup>The corresponding monobenzothiazole was formed.
CH₂Cl₂ has been reported. However, the use of DCC, pyridine and the conversion of the carboxylic acids to acid fluorides do not make this method attractive as all of these reagents are toxic. The mercapto group of 1 reacts with CH₂Cl₂ and led to the formation of the corresponding chloromethyl ether as the major side reaction. No desired product was obtained during the reaction with phthalic acid fluoride with 1 in the presence of triethylamine in 1:10.

In conclusion, the present work describes an efficient and new methodology for synthesis of 2-substituted benzothiazoles from carboxylic acids through in situ formation of acid chloride in a one pot reaction under acid-free and catalyst-free conditions.

One-Pot Synthesis of Benzothiazoles from Carboxylic Acids;
General Procedure
Phenylacetic acid (340 mg, 2.5 mmol) was treated with SOCl₂ (357 mg, 0.268 mL, 2.5 mmol) in toluene (5 mL) followed by stirring (magnetically) at r.t. for 1 h. The mixture was diluted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with H₂O (3 × 5 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford 2-(4-chlorophenoxymethyl)benzothiazole (750mg).

Scale up of 2-(4-Chlorophenoxymethyl)benzothiazole
4-Chlorophenoxyacetic acid (3.72 g, 20 mmol) was treated with SOCl₂ (2.5 g, 2.13 mL, 20 mmol) in toluene (50 mL) followed by stirring (magnetically) at r.t. for 2 h. The mixture was diluted with EtOAc (25 mL) and sat. aq NaHCO₃ (20 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with H₂O (3 × 25 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford 2-(4-Chlorophenoxymethyl)benzothiazole (4.91 g, 89%) after crystallization from EtOAc and hexane mixture (1:1). The physical data of new compounds are provided below.

2-(3-Phenylpropyl)benzothiazole
Yellow oil.
IR (neat): 3368, 2921, 1602, 1578, 1514, 1434, 1286, 1241, 1158, 1114 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.96 (d, J = 8.06 Hz, 1 H), 7.77 (d, J = 7.92 Hz, 1 H), 7.43–7.38 (m, 1 H), 7.34–7.16 (m, 6 H), 3.09 (t, J = 7.54 Hz, 2 H), 2.72 (t, J = 7.37 Hz, 2 H), 2.17 (quint, J = 7.4 Hz, 2 H).

13C NMR (300 MHz, CDCl₃): δ = 171.66, 141.10, 132.02, 131.27, 128.34, 128.28, 125.88, 125.77, 124.55, 122.35, 121.34, 34.99, 33.46, 30.96.

MS (Cl): m/z = 254 [M + H⁺].

1-(4-Hydroxy-3,5-dimethoxyphenyl)benzothiazole
Mp 132–134 °C.
IR (KBr): 3057, 2919, 1598, 1525, 1492, 1454, 1365, 1315, 1286, 1211, 1167, 1146, 1074, 1018 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.90 (d, J = 8.04 Hz, 1 H), 7.87 (d, J = 7.76 Hz, 1 H), 7.75 (s, 1 H), 7.62 (d, J = 8.32 Hz, 1 H), 7.48 (t, J = 7.31 Hz, 1 H), 7.37 (t, J = 7.50 Hz, 1 H), 6.96 (d, J = 8.36 Hz, 1 H), 4.03 (s, 3 H), 3.96 (s, 3 H).

13C NMR (300 MHz, CDCl₃): δ = 167.92, 154.03, 151.53, 149.29, 134.92, 126.57, 126.21, 124.85, 122.77, 121.47, 121.12, 110.96, 109.72, 56.00.

MS (CI): m/z = 272 [M + H⁺].

2-(4-Hydroxy-3,5-dimethoxyphenyl)benzothiazole
Mp 142–144 °C.
IR (KBr): 3480, 2938, 1614, 1529, 1481, 1451, 1427, 1366, 1334, 1282, 1211, 1199 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.03 (d, J = 8.04 Hz, 1 H), 7.87 (d, J = 7.79 Hz, 1 H), 7.47 (t, J = 7.60 Hz, 1 H), 7.38–7.34 (m, 3 H), 6.01 (s, 1 H, OH, exchangeable with D₂O), 3.99 (s, 6 H).

13C NMR (300 MHz, CDCl₃): δ = 168.13, 154.07, 147.35, 137.71, 134.82, 126.25, 125.11, 124.87, 122.85, 121.54, 121.48, 106.64, 56.59.

MS (CI): m/z = 288 [M + H⁺].

2-(4-Chlorophenoxyethyl)benzothiazole
Mp 105–107 °C.
IR (KBr): 3057, 2919, 1598, 1525, 1492, 1454, 1365, 1315, 1286, 1249, 1188, 1172, 1096, 1048, 1009, 819 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.03 (d, J = 8.07 Hz, 1 H), 7.90 (d, J = 7.94 Hz, 1 H), 7.53–7.48 (m, 1 H), 7.41 (t, J = 7.56 Hz, 1 H), 7.25 (d, J = 8.93 Hz, 2 H), 6.96 (d, J = 8.93 Hz, 2 H), 5.46 (s, 2 H).

13C NMR (300 MHz, CDCl₃): δ = 167.75, 156.26, 152.79, 134.90, 129.45, 126.76, 126.15, 125.27, 123.07, 121.72, 116.15, 67.95.

MS (CI): m/z = 276 [M + H⁺].
Anal. Calcld for C₁₅H₁₄NO₂S: C, 60.98; H, 3.66; N, 5.08. Found: C, 61.21; H, 3.58; N, 5.12.

2-Naphthalen-2-ylbenzothiazole
Mp 124–126 °C.
IR (KBr): 3048, 2922, 2856, 1594, 1497, 1450, 1428, 1362, 1306, 1270, 1174, 1123, 983, 934, 879, 860 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 8.51 (s, 1 H), 8.16 (d, J = 8.53 Hz, 1 H), 8.09 (d, J = 8.10 Hz, 1 H), 7.92–7.81 (m, 4 H), 7.51–7.45 (m, 3 H), 7.37–7.32 (m, 2 H).

References


