A RAPID AND HIGH-YIELDING SYNTHESIS OF THIAZOLES AND AMINOTHIAZOLES USING TETRABUTYLAMMONIUM SALTS

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Abstract — A convenient method for the synthesis of thiazoles and aminothiazoles by treatment of phenacyl bromides with thioamides/thiourea in the presence of tetrabutylammonium hexafluorophosphate (Bu₄NPF₆) at room temperature was developed. The products having high yields were formed rapidly (within 15 min). The method is simple, rapid and practical, generating thiazole derivatives in excellent isolated yields. The structures of the newly synthesized products were identified by FT-IR, ¹H NMR, ¹³C NMR spectroscopy and elemental analysis data.

Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. For example, the thiazolium ring present in vitamin B₁ serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids.¹ This heterocyclic system has a broad application in drug developments for the treatment of inflammation,² hypertension,³ bacterial,⁴ and HIV infections.⁵ Especially, aminothiazoles are known to be ligands of estrogen receptors⁶ as well as a novel class of adenosine receptor antagonists.⁷

In view of the importance of thiazole and its derivatives, several methods for the synthesis of thiazole derivatives were developed. The most widely used method is Hantzsch synthesis,⁸,⁹ involving the reactions of α-halo carbonyl compounds with thiourea or thioamide derivatives. Recently, many improved methods have been reported for the synthesis of thiazoles by using catalysts such as ammonium-12-molybdophosphate in methanol,¹⁰ β-cyclodextrin in water,¹¹ iodine,¹² 1,3-di-alkylimidazolium salts¹³ and by the use of microwave in ethanol.¹⁴ However, in spite of their potential utility, some of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields and often expensive catalysts.

We, herein, present an improved method for the synthesis of thiazoles, 2-amino and 2-alkyl derivatives, from treatments of phenacyl bromides with thioamide/thiourea derivatives by using Bu₄NPF₆ as a catalyst.
The reactions were carried out at room temperature and the high yield products were formed within 15 min. The obtained structures were settled from their spectral (1H and 13C NMR) data.

Thiazole derivatives in high yield were obtained from the treatments of phenacyl bromides and thiourea/thioamide derivatives with Bu₄NPF₆ at ambient temperature (Scheme 1).

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
\text{1} & \quad + \\
\text{H}_2\text{N} & \quad \text{S} \\
\text{2 : } R = \text{Me} & \quad \text{Ar} \quad \text{N} \\
& \quad \text{NH}_2 \\
& \quad \text{NMe}_2 \\
& \quad \text{Ph} \\
& \quad \text{NHCH}_2\text{Ph} \\
& \quad \text{NHCH}_2\text{CH}_2\text{Ph} \\
\text{Bu}_4\text{NPF}_6, \text{MeOH} & \quad \text{rt, 13-15 min.} \\
& \quad \rightarrow \\
& \quad \text{3} \\
& \quad \text{Ar} \quad \text{S} \\
& \quad \text{N} \\
& \quad \text{R} \\
& \quad \text{88-96 \%}
\end{align*}
\]

Scheme 1. Synthesis of thiazole derivatives in the presence of catalyst

The catalyzed reaction time and yield, and also melting points of the obtained products are given in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Thiazole</th>
<th>Yielda</th>
<th>Time (min)</th>
<th>Mp (°C)</th>
<th>Lit. mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>NH₂</td>
<td>3a</td>
<td>96</td>
<td>14</td>
<td>150-151</td>
<td>15015</td>
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<tr>
<td>2</td>
<td>C₆H₅</td>
<td>Me</td>
<td>3b</td>
<td>95</td>
<td>15</td>
<td>67-68</td>
<td>6716</td>
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<tr>
<td>3</td>
<td>p-F-C₆H₄</td>
<td>NH₂</td>
<td>3c</td>
<td>94</td>
<td>13</td>
<td>101-102</td>
<td>102-10317</td>
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<tr>
<td>4</td>
<td>p-F-C₆H₄</td>
<td>Me</td>
<td>3d</td>
<td>93</td>
<td>14</td>
<td>184-185</td>
<td>18518</td>
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<td>5</td>
<td>p-Cl-C₆H₄</td>
<td>NH₂</td>
<td>3e</td>
<td>93</td>
<td>15</td>
<td>163-164</td>
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<tr>
<td>6</td>
<td>p-Cl-C₆H₄</td>
<td>Me</td>
<td>3f</td>
<td>89</td>
<td>14</td>
<td>111-112</td>
<td>11119</td>
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<tr>
<td>7</td>
<td>p-Br-C₆H₄</td>
<td>NH₂</td>
<td>3g</td>
<td>94</td>
<td>15</td>
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<td>8</td>
<td>p-Br-C₆H₄</td>
<td>Me</td>
<td>3h</td>
<td>88</td>
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<td>130-131</td>
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<tr>
<td>9</td>
<td>p-Me-C₆H₄</td>
<td>NH₂</td>
<td>3i</td>
<td>91</td>
<td>15</td>
<td>124-125</td>
<td>124-12521</td>
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<tr>
<td>10</td>
<td>p-Me-C₆H₄</td>
<td>Me</td>
<td>3j</td>
<td>92</td>
<td>15</td>
<td>58-60</td>
<td>58-5919</td>
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<tr>
<td>11</td>
<td>p-MeO-C₆H₄</td>
<td>NH₂</td>
<td>3k</td>
<td>89</td>
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<td>12</td>
<td>p-MeO-C₆H₄</td>
<td>Me</td>
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<td>C₆H₄-O-C₆H₄</td>
<td>NH₂</td>
<td>3m</td>
<td>94</td>
<td>15</td>
<td>65-67</td>
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</tr>
<tr>
<td>14</td>
<td>C₆H₄-O-C₆H₄</td>
<td>Me</td>
<td>3n</td>
<td>92</td>
<td>14</td>
<td>67-68</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>C₆H₄-O-C₆H₄</td>
<td>NMe₂</td>
<td>3p</td>
<td>89</td>
<td>13</td>
<td>154-155</td>
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<td>C₆H₄-O-C₆H₄</td>
<td>Ph</td>
<td>3r</td>
<td>93</td>
<td>15</td>
<td>127-128</td>
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<td>C₆H₄-O-C₆H₄</td>
<td>NHCH₂Ph</td>
<td>3s</td>
<td>94</td>
<td>14</td>
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<td>-</td>
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<td>18</td>
<td>C₆H₅</td>
<td>NHCH₂CH₂Ph</td>
<td>3t</td>
<td>92</td>
<td>15</td>
<td>116-117</td>
<td>116-11722</td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography.
We also examined various tetrabutylammonium salts given in Table 2 to investigate the efficiency of the catalyst. When tetrabutylammonium hexafluorophosphate was used, it was observed that conversion of phenacyl halides into thiazoles occurred in a shorter reaction time and higher yield according to other tetrabutylammonium salts.

The significant enhancement in the rate of reaction has been attributed to basicity of anions as depicted in the previous study.\textsuperscript{22} Indeed, the nature of the anion governing the electrophilicity of the tetrabutylammonium cation led to the remarkable rate accelerations.

The amount of catalysts used in the reaction did not have any significant influence on the overall rate of the reaction and yields of products. This was confirmed by scaling up the concentration from the present 10% solids (w/v) to 15% and 20% solids (w/v) in the case of 3m and 3n compounds, respectively. The reactions went to completion in identical times and with the same isolated yields as for the diluted reaction mixture.

Table 2. Conversion of phenacyl bromide using different tetrabutylammonium salts as catalyst

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Thiazole 3a</th>
<th>Thiazole 3c</th>
<th>Thiazole 3h</th>
<th>Thiazole 3k</th>
<th>Thiazole 3n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu$_4$NPF$_6$</td>
<td>14</td>
<td>96</td>
<td>13</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td>Bu$_4$NF$_4$</td>
<td>22</td>
<td>89</td>
<td>21</td>
<td>86</td>
<td>25</td>
</tr>
<tr>
<td>Bu$_4$NCl</td>
<td>22</td>
<td>88</td>
<td>23</td>
<td>88</td>
<td>23</td>
</tr>
<tr>
<td>Bu$_4$NBr</td>
<td>23</td>
<td>86</td>
<td>22</td>
<td>85</td>
<td>24</td>
</tr>
<tr>
<td>Bu$_4$NI</td>
<td>21</td>
<td>89</td>
<td>24</td>
<td>87</td>
<td>23</td>
</tr>
</tbody>
</table>

* $t$= time (min), $y$= yield (%)  

Several phenacyl bromides given in Table 2 exhibited smooth reactions with thiourea and thioacetamide to give substituted 2-amino-4-arylthiazole and 2-methyl-4-arylthiazole, respectively. As can be seen in Table 2, the reactions were efficiently completed at ambient temperature under mild conditions to afford the corresponding thiazoles in excellent yields in all cases. Also, we did not obtain any difference among the phenacyl bromides substituted by electron-donating or electron-withdrawing groups. The obtained products were characterized by $^1$H and $^{13}$C NMR spectroscopy, FT-IR, melting point and elemental analyses.

The $^1$H NMR spectra of 3s and 3m compounds show peaks as broad singlets at $\delta$ 5.04 and 5.12 ppm respectively, which correspond to the amino group. The characteristic peaks appearing at $\delta$ 6.48–6.62 ppm correspond to C5–H of the thiazole ring for all compounds. In the $^{13}$C NMR spectra, the peaks appearing in the range of $\delta$ 169–171 ppm correspond to C2 of the thiazole ring. The FT-IR spectra of 3m and 3s compounds show peaks at 3448 and 3459 cm$^{-1}$ corresponding to the amino group. In the case of 3n
and 3p compounds, the peaks corresponding to the methyl group appeared at 3019-2835 cm\(^{-1}\). For the compounds synthesized previously (compounds 3a-3l and 3t in Table 1), the obtained values were in agreement with those reported in the literature.

Methanol was chosen as the most available solvent for the catalyzed reactions among the polar solvents, because the reaction was sluggish in the others, such as dichloromethane and chloroform. It was also noted that the reaction did not proceed in nonpolar solvents such as hexane and toluene even after stretching the reaction time (24 h).

N-Phenethyl-4-phenylthiazol-2-amine, commonly known as fanetizole is an anti-inflammatory agent that was reported to have reached phase II clinical trails for the treatment of rheumatoid arthritis. Generally, fanetizole has been synthesized by using stringent reaction conditions such as microreactors and heating in solvents, such as DMF and NMP. We presented a novel procedure for the synthesis of the anti-inflammatory drug fanetizole (compound 3t). In this procedure, we treated phenacyl bromide with 2-phenylethyl thiourea in methanol by using Bu\(_4\)NPF\(_6\) as a catalyst to afford fanetizole in 92% yield in 15 min at ambient temperature.

EXPERIMENTAL

Materials and methods

\(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker DPX-400 spectrometer in CDCl\(_3\) using TMS as internal standard. Infrared spectra were recorded with Perkin-Elmer 1605 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a LECO-CHNS-932 instrument. Melting points were measured by using a EZ-Melt Automated MPA 120 melting point apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck, Fluka and Sigma. Column chromatography was performed using silica gel (60–120 mesh size).

General procedure for the synthesis of thiazole derivatives

A mixture of phenacyl bromide 1 (1 mmol), thioamide/thiourea 2 (1.2 mmol) and Bu\(_4\)NPF\(_6\) (10 mol%) was stirred in MeOH (5 mL) at room temperature under vigorous magnetic stirring. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel using hexane-EtOAc (4:1) as eluent to afford pure product.

4-(4-Phenoxyphenyl)thiazol-2-amine (3m)

White solid; mp 65–67 °C; FT-IR (KBr): 3459, 3244, 3016, 2202, 2048, 1673, 1626, 1543, 1522, 1491, 1456, 1329, 973, 761 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=\) 5.12 (br s, 2H, NH\(_2\)), 6.55 (s, 1H, thiazole H), 7.14-7.72 (m, 9H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=\) 98.6, 119.2, 119.7, 124.0, 125.6, 127.9, 130.2,
145.6, 156.4, 158.5, 171.3. Anal. Calcd for C_{15}H_{12}N_{2}OS: C, 67.14; H, 4.51; N, 10.44%. Found: C, 67.49; H, 4.72; N, 10.34%.

2-Methyl-4-(4-phenoxyphenyl)thiazole (3n)
Yellow solid; mp 67–68 °C; FT-IR (KBr): 3235, 3017, 2835, 2200, 1669, 1619, 1541, 1488, 1461, 1301, 977, 756 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=2.77\) (s, 3H, CH\(_3\)), 6.51 (s, 1H, thiazole H), 7.17-7.64 (m, 9H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=19.7, 108.4, 118.0, 118.8, 121.9, 124.1, 126.2, 127.1, 128.5, 153.4, 157.0, 169.2\). Anal. Calcd for C\(_{16}\)H\(_{13}\)N\(_2\)OS: C, 71.88; H, 4.90; N, 9.24%. Found: C, 71.76; H, 4.77; N, 9.09%.

N,N-Dimethyl-4-(4-phenoxyphenyl)thiazol-2-amine (3p)
White solid; mp 154–155 °C; FT-IR (KBr): 3209, 3019, 2837, 1605, 1565, 1548, 1488, 1461, 1313, 759 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=3.12\) (s, 6H, CH\(_3\)), 6.48 (s, 1H, thiazole H), 7.11-7.66 (m, 9H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=41.0, 105.0, 117.6, 117.9, 121.5, 124.0, 125.4, 127.2, 127.9, 150.2, 157.0, 170.1\). Anal. Calcd for C\(_{17}\)H\(_{16}\)N\(_2\)OS: C, 68.89; H, 5.44; N, 9.45%. Found: C, 69.09; H, 5.06; N, 9.13%.

4-(4-Phenoxyphenyl)-2-phenylthiazole (3r)
Yellow solid; mp 127-128 °C; FT-IR (KBr): 3221, 3009, 1611, 1543, 1521, 1479, 1449, 759 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=6.46\) (s, 1H, thiazole H), 7.09-7.69 (m, 14H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=100.3, 111.4, 118.7, 119.6, 123.9, 125.4, 127.6, 129.1, 130.8, 144.9, 153.2, 156.1, 158.2, 170.4\). Anal. Calcd for C\(_{21}\)H\(_{15}\)N\(_2\)OS: C, 76.57; H, 4.59; N, 4.25%. Found: C, 76.35; H, 4.83; N, 4.03%.

N-Benzyl-4-(4-phenoxyphenyl)thiazol-2-amine (3s)
Yellow solid; mp 137-138 °C; FT-IR (KBr): 3448, 3196, 3010, 2824, 1618, 1552, 1539, 1477, 1454, 1318, 753 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta=4.41\) (s, 2H, CH\(_2\)), 5.04 (br s, 1H, NH), 6.62 (s, 1H, thiazole H), 6.89-7.46 (m, 14H, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta=49.0, 114.3, 116.1, 118.7, 121.4, 126.8, 128.4, 139.9, 152.4, 152.6, 157.1\). Anal. Calcd for C\(_{22}\)H\(_{18}\)N\(_2\)OS: C, 73.71; H, 5.06; N, 7.82%. Found: C, 73.34; H, 4.99; N, 7.39%.

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