An Aerobic Oxidative Coupling Approach for the Synthesis of N-substituted 2-aminobenzothiazole Derivatives using Iron Catalyst

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ABSTRACT

A facile and convenient method was developed for the formation of novel N substituted 2-aminobenzothiazoles via an iron-catalysed condensation of 2-aminobenzothiazole with different amines. This method is applicable for a wide range of aliphatic, aromatic and heterocyclic amines furnishing moderate yields of the corresponding products and thus rendering the methodology as a highly eco-friendly, inexpensive alternative to the existing methods.

Keywords: 2-Aminobenzothiazole, N-substituted, synthesis, aerobic oxidative coupling, Iron catalyst.

INTRODUCTION

Substituted benzothiazoles exhibits various biological and therapeutical activities\(^1\)\(^2\) Aminobenzothiazoles are synthesised by employing various catalysts: cobalt was used by Zhu\(^3\)\(^4\), palladium by Vera\(^5\), copper by Saha\(^6\) and Khatun\(^7\), nano copper oxide\(^8\)\(^9\). Other methods of synthesising aminobenzothiazoles is by Herz method\(^10\), solid phase synthesis\(^11\), using benzyltrimethylammonium tribromide\(^12\) or sodium dichlorodioate\(^13\), starting from o-nitroaniline\(^14\) or in water\(^15\). Apart from synthesis, following biological activities were reported: Aurora-A kinase inhibitor\(^16\), calcium channel blockers\(^17\), anti-cancer\(^18\)\(^19\), herbicidal activity\(^20\), mitochondrial apoptotic inducers\(^21\), neuronal nitric oxide synthase inhibitor\(^22\), anti-inflammatory\(^23\)\(^24\), antimalarials\(^25\), antimicrobial\(^26\)\(^27\).

Oxidative coupling reactions with amines are reported in literature. Zhou et al\(^28\)\(^29\) used boron-dipyrromethene (BODIPY) under mild condition, Yu et al\(^30\) used oxone and trifluoroacetic acid in PEG-400 for the green method. Also, various metals are used for these conversions: gold\(^31\), gold nanoparticle\(^32\), copper\(^33\), silica supported vanadium\(^34\), ruthenium\(^35\) and cobalt\(^36\).
Synthesis of N-substituted amines reported in literature does not use iron as catalyst. In view of these reports and literature, attempt was made to synthesize novel N-substituted aminobenzothiazole derivatives using iron as catalyst via oxidative coupling route.

RESULTS AND DISCUSSION

Different iron compounds (FeCl₃, FeCl₂, FeCl₂.2H₂O, FeSO₄.7H₂O, Fe(OAc)₂ and FeBr₂) were used for the optimisation. The reactions (scheme-1) were carried out with 10% mol of the catalyst and found that FeBr₂ results in 63% yield. Therefore, concentration of the catalyst was further reduced to 5% and 2%. This resulted in 64 and 29% yields respectively. Also the effect of the inert medium was evaluated by using N₂ and Ar environment and that resulted in 6 and 3% yields respectively. Hence the concentration of FeBr₂ was optimised at 5% mol.

While optimising the concentration of the catalyst, the reactants were used 1.5 equivalents of aminobenzothiazole and 1 equivalent of benzylamine. After finalising the concentration of the catalyst, the reactants concentrations were changed to 1 and 2 equivalents respectively and the yield obtained was only 48%.

It has been found that FeBr₂ gave better yields amongst all other iron catalysts used. To optimise the conditions, different concentrations were used and 5% mol found to be the optimum concentration without the usage of inert conditions (Table-1). To substantiate our proposed mechanism (scheme - 3), we have carried out the reactions in inert conditions. During the process, oxygen starved environment has yielded very low product.

Under these optimised conditions, various N-substituted 2-aminobenzothiazoles (3a - e) were synthesised from their corresponding amine (2a - e) and 2-amino benzothiazole (1) (scheme – 2). These newly synthesised compounds were characterised by IR, NMR and MS. In order to cross check applicability for different amines, aromatic,

![Scheme 1: Reaction scheme for the optimisation of the reaction conditions](image)

**Table 1: Optimisation Parameters For The Synthesis Of N-Substituted Aminobenzothiazoles**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (% mol)</th>
<th>Environment, (%mol of 2 amino benzothiazole : %mol of Benzylamine)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeCl₃ (2% mol)</td>
<td>Air, (1.5:1)</td>
<td>Traces</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂ (10% mol)</td>
<td>Air, (1.5:1)</td>
<td>Traces</td>
</tr>
<tr>
<td>3</td>
<td>FeCl₂.2H₂O (10% mol)</td>
<td>Air, (1.5:1)</td>
<td>Not recovered</td>
</tr>
<tr>
<td>4</td>
<td>FeSO₄.7H₂O (10% mol)</td>
<td>Air, (1.5:1)</td>
<td>Not recovered</td>
</tr>
<tr>
<td>5</td>
<td>Fe(OAc)₂ (10% mol)</td>
<td>Air, (1.5:1)</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>FeBr₂ (10% mol)</td>
<td>Air, (1.5:1)</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>FeBr₂ (5% mol)</td>
<td>Air, (1.5:1)</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>FeBr₂ (2% mol)</td>
<td>Air, (1.5:1)</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>FeBr₂ (10% mol)</td>
<td>N₂, (1.5:1)</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>FeBr₂ (10% mol)</td>
<td>Ar, (1.5:1)</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>FeBr₂ (10% mol)</td>
<td>Air, (2:1)</td>
<td>Not recovered</td>
</tr>
<tr>
<td>12</td>
<td>No catalyst</td>
<td>Air, (1.5:1)</td>
<td>Not recovered</td>
</tr>
</tbody>
</table>
aliphatic and heterocyclic substrates were employed and produced moderate yields.

Here we are reporting the iron as catalyst via oxidative coupling approach for the synthesis of novel N-substituted aminobenzothiazole derivatives (3 a – e).

**General procedure**

Iron catalyst was added to a two-necked, round-bottom flask containing the 2-aminobenzothiazole and an amine at room temperature. The resulting reaction mixture was heated at 110°C for 24 h. The progress of the reaction was monitored by TLC. After 24 hours, the reaction mixture was directly purified using column chromatography.

N-benzylbenzo[d]thiazol-2-amine (3a): The title compound was synthesised as per the general method using benzyl amine. Yield: 64%. Mp: 244-246°C. ¹H NMR (400 MHz, DMSO-d₆): δ 8.52 (s, 1H, NH), 7.68 – 7.00 (m, 9H, aromatic), 4.60 (s, 2H, CH₂). ¹³C NMR (75 MHz, DMSO-d₆): δ 166.6, 158.8, 152.9, 131.2, 130.8, 129.3, 125.9, 121.4, 118.5, 48.7. Mol Wt: 240.32, m/z: 240.09. Anal. Calcd for C₁₄H₁₂N₂S: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.05; H, 5.29; N, 11.80; S, 12.85.

N-(4-methoxybenzyl)benzo[d]thiazol-2-amine (3b): The title compound was synthesised as per the general method using 4-methoxybenzyl amine. Yield: 67%. Mp: 296-298°C. ¹H NMR (400 MHz, DMSO-d₆): δ 8.43 (s, 1H, NH), 7.67 - 6.89 (m, 8H, aromatic), 4.51 (s, 2H, CH₂), 3.73 (s, 3H, OCH₃). ¹³C NMR (75 MHz, DMSO-d₆): δ 166.6, 158.8, 152.9, 131.2, 130.8, 129.3, 125.9, 121.4, 118.5, 114.2, 55.5, 47.2. Mol Wt: 270.35, m/z: 270.21. Anal. Calcd for C₁₅H₁₄N₂OS: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.91; H, 5.34; N, 10.41; S, 11.46.

N-(4-methoxybenzyl)benzo[d]thiazol-2-amine (3b): The title compound was synthesised as per the general method using 4-methoxybenzyl amine. Yield: 67%. Mp: 296-298°C. ¹H NMR (400 MHz, DMSO-d₆): δ 8.43 (s, 1H, NH), 7.67- 6.89 (m, 8H, aromatic), 4.51 (s, 2H, CH₂), 3.73 (s, 3H, OCH₃). ¹³C NMR (75 MHz, DMSO-d₆): δ 166.6, 158.8, 152.9, 131.2, 130.8, 129.3, 125.9, 121.4, 118.5, 114.2, 55.5, 47.2. Mol Wt: 270.35, m/z: 270.21. Anal. Calcd for C₁₅H₁₄N₂OS: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.91; H, 5.34; N, 10.41; S, 11.46.

**Scheme 2:**

**Scheme 3: Possible mechanism**
N-butylbenzo[d]thiazol-2-amine (3c): The title compound was synthesised as per the general method using n-butyl amine. Yield: 72%. Mp: 199-201ºC. 1H NMR (400 MHz, DMSO - d6): δ 8.06 (s, 1H, NH), 7.96 - 7.08 (m, 4H, aromatic), 3.56 – 3.48 (t, 2H, NHCH2), 1.52 to 1.33 (m, 4H, CH2-CH2), 0.91 (t, 3H, CH3). 13C NMR (75 MHz, DMSO - d6): δ 166.6, 153.4, 130.8, 125.8, 121.4, 121.2, 118.4, 47.7, 40.5, 39.7, 39.4. Mol Wt: 206.31, m/z = 206.10. Anal. Calcd for C11H14N2S: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found C, 64.24; H, 6.99 N, 13.67; S, 15.08.

N-octylbenzo[d]thiazol-2-amine (3d): The title compound was synthesised as per the general method using n-octyl amine. Yield: 75%. Mp: 233-235ºC. 1H NMR (400 MHz, DMSO - d6): δ 7.99 (s, 1H, NH), 7.65 - 6.97 (m, 4H, benzothiazol), 3.36 – 3.31 (t, 2H, NHCH2), 1.61 - 1.26 (m, 12H, CH2), 0.87 – 0.84 (t, 3H, CH3). 13C NMR (75 MHz, DMSO - d6): δ 166.6, 153.4, 130.8, 125.9, 121.2, 121.2, 118.3, 47.7, 40.8, 40.5, 40.0, 39.7, 39.4, 39.2. Mol Wt: 262.41, m/z = 262.01. Anal. Calcd for C15H22N2S: C, 68.66; H, 8.45; N, 10.68; S, 12.22. Found: C, 68.87; H, 8.57; N, 10.93; S, 11.63.

N-(thiophen-2-ylmethyl)benzo[d]thiazol-2-amine (3e): The title compound was synthesised as per the general method using 2-(Aminomethyl)thiophene. Yield: 59%. Mp: 199-201ºC. 1H NMR (400 MHz, DMSO - d6): δ 8.22 (s, 1H, NH), 7.51 – 6.98 (m, 7H, aromatic), 4.48 (s, 2H, CH2). 13C NMR (75 MHz, DMSO - d6): δ 166.6, 158.6, 152.8, 141.2, 131.4, 130.8, 129.3, 126.6, 125.9, 121.4, 118.5, 51.7. Mol Wt: 246.35, m/z = 246.09. Anal. Calcd for C12H10N2S2: C, 58.51; H, 4.09; N, 11.37; S, 26.03. Found: C, 58.67; H, 4.21; N, 11.42; S, 25.69.

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