Synthesis of benzothiazole appended β-lactams through [2+2]-cycloaddition reaction

Arasampattu S Nagarajan, D Kathirvelan, M Pramesh & Boreddy S R Reddy

aIndustrial Chemistry Laboratory, Central Leather Research Institute, Chennai 600 020, India
bDepartment of Chemistry, A.V.V. M, Sri Pushpam College, Poondi 613 503, India
E-mail: bsrreddy.clri@gmail.com

Received 8 December 2009; accepted (revised) 7 September 2010

A simple and convenient protocol for the synthesis of benzothiazole appended β-lactams is described. This methodology involves [2+2]-cycloaddition of benzothiazole substituted imines with chloroacetyl chloride (CAC) in the presence of triethylamine to yield the corresponding product in moderate to good yields. The reaction is compatible with a wide variety of functional groups.

Keywords: Benzothiazole, imine, [2+2]-cycloaddition, azetidin-2-one

There has been considerable interest during this decade in the synthesis of substituted or fused benzothiazoles because benzothiazole motif is an important skeleton in the naturally occurring biologically active compounds. Added to this, benzothiazole is having potent biological properties such as antitumor, antimicrobial and LTD₄ receptor antagonist like orexin. Arylbenzothiazoles bearing a substituent at C-2 are of great interest as these structural frameworks have proved to be an important class of bicyclic privileged substructures owing to their utility as imaging agents for β-amyloid, chemiluminescent agents, anti-tumour agents, calcium channel antagonists, antituberculosis, antiparasitics and also as photosensitizers.

Results and Discussion

As part of our endeavour to synthesize new 2-substituted aryl benzothiazoles of biocidal interest, and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably. On the other hand, the chemistry of β-lactams played an important role in the medicinal organic chemistry since the discovery of penicillin (Figure 1 B) in 1928 and shortly after that the development of cephalosporin (Figure 1 C) compounds. Also, β-lactam also possess cholesterol absorption inhibitory activity as well as antithrombotic, antiviral and antifungal activities. Therefore, to fuse β-lactam moiety in C-2 position of benzothiazole is focused.

Despite numerous methods reported for the synthesis of β-lactams, cycloaddition is the most simple and effective method for the synthesis of β-lactams from imines and acid chlorides in the presence of a mild base. Some reports are available on the cycloaddition that require high temperature and prolonged reaction time. Moreover, cycloaddition reaction leads to the formation of various by products.

Here, we have reported a convenient synthetic route for 1-(4-benzothiazol-2-yl-phenyl)-4-phenyla-zetidin-2-one derivatives through [2+2] cycloaddition reaction.
reaction of imine generated from benzothiazole substituted aniline with 4-hydroxy aldehydes and chloroacetyl chloride (Scheme I).

It is observed that no product was formed without a base catalyst even after stirring for 4 hr. Therefore, various organic/inorganic bases for cycloaddition reaction and triethylamine have been studied and was found to be the best of choice Table I. Tertiaryamine balances the nucleophilicity and basicity, which is perhaps a key factor that required for the cycloaddition reaction to occur efficiently. The isolation of the product was pretty much straightforward as the solid product precipitated which was filtered, washed with water and dried to afford pure product (1H NMR). The scope of the substrate in the reaction under the optimized reaction conditions was investigated and the results are summarized in Table II. The reaction was amenable to a wide variety of substituted ketenes. The nature of functional groups in the aromatic ring of the aldehyde exerted greater influence on the final product. An increase in the yield was observed with aryl aldehydes bearing electron-donating group.

In conclusion, a simple and efficient protocol for the synthesis of substituted 1-(4-benzothiazol-2-yl-phenyl)-4-phenylazetidin-2-one derivatives using triethylamine as a catalyst has been developed. This methodology offers several advantages including: (a) simple experimental procedure, (b) milder reaction conditions, (c) high yield, (d) general applicability and easy isolation of products without employing any purification techniques like column chromatography and recrystallization.

**Experimental Section**

Melting points are determined with a Buchi 512 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer FT-IR. Both 1H and 13C NMR were recorded in DMSO-d6 using JEOL and Bruker 300-MHz high resolution NMR spectrometers using TMS as an internal standard. The masses are analysed by using a electron spray ionisation method with Thermo Fennigan mass spectrometer. Elemental analyses were recorded using Thermo Finnigan FLASH EA 1112 CHN analyzer. TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-nagel.Germany). Aminobenzothiazole and the corresponding Schiff bases of benzothiazole are prepared as per the literature procedures11,12.

**Typical procedure for the synthesis of substituted azetidin-2-one derivatives**

The imine (5.0 mmole) was placed in a 50 mL round bottom flask equipped with a magnetic pallet...
<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Product(^a)</th>
<th>Time (hr)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Imine" /></td>
<td><img src="image2" alt="Product" /></td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Imine" /></td>
<td><img src="image4" alt="Product" /></td>
<td>11</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Imine" /></td>
<td><img src="image6" alt="Product" /></td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Imine" /></td>
<td><img src="image8" alt="Product" /></td>
<td>13</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Imine" /></td>
<td><img src="image10" alt="Product" /></td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Imine" /></td>
<td><img src="image12" alt="Product" /></td>
<td>18</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Imine" /></td>
<td><img src="image14" alt="Product" /></td>
<td>21</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Imine" /></td>
<td><img src="image16" alt="Product" /></td>
<td>24</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\) All products are characterized by IR, NMR, and mass spectrometry

\(^b\) Isolated Yield
and nitrogen atmosphere, followed by the addition of 1, 4-dioxane (10 mL) and triethyl amine (4 drops, 0.2 mL) at RT while stirring for about 1 hr. The resulting mixture was cooled to 0-5ºC, and monochloroacetyl chloride (6 mmole) was added over 5-10 min keeping the internal temperature below 10ºC. After the addition was completed, the reaction was warmed to RT and then refluxed for 6 hr. After the completion of the reaction, as confirmed by the TLC, reaction-mixture was cooled to RT and poured into crushed ice and neutralized with 5% sodium bicarbonate solution in water. The precipitated solid was filtered and washed with cold water (3 × 15 mL) and 5% ethyl acetate in pet. ether (20 mL) and dried.

1-(4-Benzothiazol-2-yl-phenyl)-4-(4-chloro-phenyl)azetidin-2-one

(Entry 1, Table II) Yellow solid, m.p. 201-05ºC; IR (KBr): 748, 831, 1429, 1475, 1604, 1712, 2936 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.23 (d, 2H, J = 5.4 Hz), 4.81 (t, 1H ), J = 6.0 Hz), 7.27 (m, 6H), 7.69 (d, 2H, J = 8.4 Hz), 7.82 (d, 2H, J = 7.8 Hz) and 7.95 (d, 2H, J = 7.7 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 37.2, 59.4, 119.4, 122.3, 123.16, 126.42, 127.63, 128.91, 130.23, 132.62, 133.42, 134.1, 142.66, 142.87, 155.21, 169.33 and 170.1; ESI-MS: 372 (M+). Anal. Calcd for C₂₅H₁₅N₂O₂S: C, 70.57; H, 3.41; N, 7.17. Found: C, 67.53; H, 3.77; N, 7.11%.

1-(4-Benzothiazol-2-yl-phenyl)-4-(2-hydroxy-phenyl)azetidin-2-one

(Entry 2, Table II) Light yellow solid m.p. 213-15ºC; IR (KBr): 744, 841, 1421, 1467, 1611, 1752 and 2933 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.20 (d, 2H, J = 5.4Hz), 4.79 (t, 1H ), J = 6.0 Hz), 7.12 (m, 7H), 7.73 (d, 2H, J = 8.2 ), 7.93 (d, 3H, J = 7.3 ) and 8.17 (d, 2H, J = 7.8); ¹³C NMR (75 MHz, DMSO-d₆): δ 37.2, 59.41, 119.43, 122.3, 123.13, 126.4, 127.64, 128.92, 130.21, 132.62, 133.43, 134.14, 142.67, 142.83, 155.22, 169.31 and 170.1; ESI-MS: 404 (M+). Anal. Calcd for C₂₅H₁₃F₂N₂O₂S: C, 68.30; H, 4.24; N, 6.93. Found: C, 69.10; H, 4.19; N, 6.79%.

1-(4-Benzothiazol-2-yl-phenyl)-4-(2-hydroxy-phenyl)azetidin-2-one

(Entry 5, Table II) Colourless solid m.p. 213-15ºC; IR (KBr): 749, 851, 1427, 1465, 1614, 1732, 2956 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.27 (d, 2H, J = 5.4 ), 4.80 (t, 1H ), 7.12 (m, 7H), 7.86 (d, 2H, J = 8.1), 7.92 (d, 2H, J = 7.9) and 8.15 (d, 2H, J = 7.2); ¹³C NMR (75 MHz, DMSO-d₆): δ 37.2, 59.41, 119.43, 122.39, 123.12, 126.44, 127.62, 128.91, 129.24, 122.6, 133.42, 134.11, 142.61, 142.83, 155.26, 169.34 and 170.01; ESI-MS: 372 (M+). Anal. Calcd for C₂₁H₁₆N₂O₂S: C, 70.95; H, 4.33; N, 7.52. Found: C, 70.79; H, 4.25; N, 7.39%.

1-(Benzo[d]thiazol-2-yl)-4-(4-fluro-phenyl)azetidin-2-one

(Entry 6, Table II) Yellow solid, m.p. 203-07ºC; IR (KBr): 739, 791, 1439, 1475, 1604, 1711, 2935 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 3.21 (d, 2H, J = 5.3 ), 4.79 (t, 1H ), J = 6.0 Hz), 7.12 (m, 5H), 7.86 (d, 2H, J = 8.4 ), 7.92 (d, 2H, J = 7.8 ) and 8.15 (d, 3H, J = 7.8 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 37.22, 59.41, 119.43, 122.32, 123.11, 126.47, 127.63, 128.92, 130.24, 132.62, 133.46, 134.11, 142.63, 142.84, 155.27, 169.37 and 170.2; ESI-MS: 374 (M+). Anal. Calcd for C₂₁H₁₃F₂N₂O₂S: C, 70.57; H, 4.04; N, 7.48. Found: C, 70.50; H, 3.41; N, 7.37%.

Acknowledgements

The authors (ASN and DK) thank DST for financial assistance (SR/SI/PC- 33/2006)

References

