A novel three-component reaction for the synthesis of 3-aryl-4H-benzo [1,4] oxazin-2-amine

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Abstract A high yielding and fast method for the synthesis of 3-aryl-4H-benzo [1,4] oxazin-2-amine via one-pot, three component reaction of an aromatic aldehyde, isocyanide and o-aminophenol using p-toluene sulfonic acid as a catalyst is described.

Keywords p-toluene sulfonic acid · 3-aryl-4H-benzo [1,4]oxazin-2-amine · One-pot · Isocyanide

Benzoazines are an important class of compounds with a benzo-fused heterocyclic ring and form the key structural element of a variety of biologically active compounds [1–3]. These compounds are valuable building blocks for the synthesis of more complex derivatives. Photochemical transformation of benzoazines to other heterocyclic structures have also been reported [4,5]. Several 3,4-dihydro-2H-1, 4-benzoxazine derivatives have been reported to be potassium channel openers (PCOs) in vascular smooth muscle [6].

Therefore, active studies for the synthetic development of benzoazine derivatives have been carried out [7–10]. We have also been interested in a new synthetic study of such benzoazine derivatives. As part of our program aimed at developing new methods for the preparation of new compounds [11], we would like to report the one-pot synthesis of 3-aryl-4H-benzo[1,4]oxazin-2-amines by three-component reaction of an aromatic aldehyde, isocyanide and o-aminophenol using p-toluene sulfonic acid as catalyst (Scheme 1).

\[ p\text{-Toluensulfonic acid (PTSA)} \text{ is a cheap, stable, and commercialy available chemical. It has been used as an efficient acid catalyst for the synthesis of 4(3H)-quinazolinones [12], the regiospecific nitration of phenols [13] and the carbonylation of formaldehyde [14]. Then we decided to use this catalyst for the synthesis of benzoazines. In a typical procedure, benzaldehyde (1 mmol), cyclohexyl isonitrile (1 mmol) with o-amino phenol (1 mmol) in the presence of a catalytic amount of p-Toluenesulfonic acid in ethanol at reflux afforded the desired 3-phenyl-4H-benzo [1,4] oxazin-2-amines (4a) in 87% yield (Entry 1, Table 1). The reaction was then applied to a variety of aromatic aldehydes resulting in good yields (see Table 1). To the best of our knowledge there are no reports on the synthesis of these compounds.} \]

Both aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl group, alkoxyl group) were employed giving expected products (4) in good to excellent yields under these reaction conditions, so we conclude that no obvious effect of electron and nature of substituents on the aromatic ring was observed. However, we found that the reaction did not proceed with aliphatic aldehydes. In order to show the generality and scope of this new protocol, we used various o-aminophenols and isocyanides in the presence of p-Toluensulfonic acid and the results obtained are summarized in Table 1. The variations in the yields were small and both substituted o-aminophenols such as 4-chloro and 4-methoxy gave expected products in good yields. A plausible mechanism for this reaction is suggested in Scheme 2. The first step may involve reaction of the aromatic aldehyde with o-aminophenol followed by isocyanide attack on the resulting intermediate to give the desired product.

In conclusion, we have described a highly efficient procedure for the preparation of 3-aryl-4H-benzo[1,4] oxazin-2-amines by a three component condensation using...
Table 1 Synthesis of 3-aryl-4H-benzo[1,4]oxazin-2-amines using various aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R′</th>
<th>Ar</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclohexyl</td>
<td>H</td>
<td>C₆H₅</td>
<td>4a</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexyl</td>
<td>H</td>
<td>4-Cl–C₆H₄</td>
<td>4b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexyl</td>
<td>H</td>
<td>3-NO₂–C₆H₄</td>
<td>4c</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexyl</td>
<td>H</td>
<td>4-NO₂–C₆H₄</td>
<td>4d</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexyl</td>
<td>H</td>
<td>4-CH₃–C₆H₄</td>
<td>4e</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>cyclohexyl</td>
<td>H</td>
<td>4-CH₃O–C₆H₄</td>
<td>4f</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>cyclohexyl</td>
<td>H</td>
<td>4-OH–C₆H₄</td>
<td>4g</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>tert-butyl</td>
<td>H</td>
<td>C₆H₅</td>
<td>4h</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>tert-butyl</td>
<td>H</td>
<td>4-CH₃O–C₆H₄</td>
<td>4i</td>
<td>88</td>
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<tr>
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<td>H</td>
<td>4-NO₂–C₆H₄</td>
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<tr>
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<td>C₆H₅</td>
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</tr>
<tr>
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<td>cyclohexyl</td>
<td>Cl</td>
<td>C₆H₅</td>
<td>4l</td>
<td>86</td>
</tr>
</tbody>
</table>

"Yield of isolated products"

PTSA as catalyst. All the proposed reactions allowed the preparation of products in good yield without further purification. The reaction products were prepared in moderate to average yield, even with different substituted aldehydes. Moreover, the procedure offers several advantages including high yields, operational simplicity and cleaner reaction which makes it a useful and attractive process for the synthesis of these compounds.

Scheme 1

Scheme 2

Preparation of 3-ary 4H-benzo[1,4]oxazin-2-amines:
typical procedure

A mixture of the aromatic aldehydes 1 (1 mmol), o-amino-phenol (1 mmol), isocyanide (1 mmol) and PTSA (0.05 g) in ethanol (5 mL) was refluxed for 6 h and then cooled to room temperature. The product was precipitated by addition of 10 mL of water. The precipitate was filtered and washed with water. The residue was crystallized from ethanol to give pure product.

N-cyclohexyl-3-phenyl-4H-benzo[1,4]oxazin-2-amines (4a)

Mp 185°C; IR (KBr) (ν<sub>max</sub>, cm<sup>-1</sup>): 3163, 3156; 1H NMR (CDCl₃, 300 MHz) δ<sub>H</sub> (ppm): 1.09–2.12 (m, 10H), 3.44 (m, 1H), 4.25 (s, 1H, NH), 4.71 (s, 1H, NH), 7.21–7.83 (m, 9H, arom). 13C NMR (CDCl₃, 125 MHz) δ<sub>C</sub> (ppm): 23.09, 24.37 (2CH₂), 28.12 (2CH₂), 47.36, 121.16 (2CH), 123.13, 123.88, 124.48, 126.19 (2CH), 127.53, 130.01, 131.02, 136.01, 137.52, 138.33, 140.44. GC/MS: 306 (M<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O: C, 78.40; H, 7.24; N, 9.14%. Found: C, 78.03; H, 7.33; N, 9.12%.