Synthesis of \(N\)-Substituted Phthalimidoalkyl 1H-1,2,3-Triazoles: a Molecular Diversity Combining Click Chemistry and Ultrasound Irradiation

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Uma série de derivados 1,2,3-triazólicos foi sintetizada a partir de \(N\)-alquilftalimida-azidas (\(A_1-A_4\)) e alcinos (a-e) sob irradiação de ultrassom na presença de CuI, Et\(_3\)N e DMF como solvente. O presente protocolo forneceu 18 novos 1,2,3-triazóis (1-4) em rendimentos de bons a excelentes (67-98%).

A series of 1,2,3-triazole derivatives was synthesized from \(N\)-phthalimidoalkyl-azides (\(A_1-A_4\)) and alkynes (a-e) under ultrasound irradiation in the presence of CuI, Et\(_3\)N and DMF as solvent. The present protocol afforded 18 new 1,2,3-triazoles (1-4) in good-to-excellent yields (67-98%).

Keywords: 1,2,3-triazole, phthalimide, ultrasound, copper-catalyst, click chemistry

Introduction

The discovery of new drugs has one of the largest beneficial effects on human health. Everyday, a variety of molecules are synthesized with this purpose, employing a myriad of protocols to attach structural part or functional groups into old or new chemical entities.

Phthalimide is a functional group of growing interests in the field of organic synthesis. In particular, our research group is interested in new derivatives of \(N\)-substituted phthalimides, a very important motif in synthetic organic chemistry for the preparation of suitable scaffolds for biological activity screening. The conjugation of phthalimide with 1,2,3-triazole has recently emerged in the literature. Herein, we consider these molecular hybrids as good candidates for pharmaceutical application.

In the last decade, 1,2,3-triazoles have become attractive as target compounds for drug discovery, among other applications. After the discovery by Meldal and co-workers and Sharpless and co-workers of the Cu-AAC (Cu-catalyzed azide alkyne cycloadditon) reaction, a number of molecules were synthesized through this method to afford the 1,4-disubstituted 1,2,3-triazoles. Due to recent application of the products resultant from Cu-AAC protocols, this reaction has encouraged many more researchers around the world. Usually, the most common methodology uses CuSO\(_4\) as Cu(II) source and sodium ascorbate in tert-BuOH-H\(_2\)O at ambient temperature. However, this procedure was altered during the last decade mainly to overcome difficulties related to low reactivity in the presence of specific functional groups. For example, our group recently reported that the catalytic system CuSO\(_4\)/sodium ascorbate acted as an undesirable copper(II)-ascorbate redox system that resulted in reduction of the electron-deficient azide group to an amine group. Another recent protocol used acidic conditions to promote the synthesis of 1,2,3-triazoles. Sonochemistry has been applied to accelerate a large number of organic reactions and enhance chemical yields. The effect of ultrasound on the “click chemistry” of 1,2,3-triazole synthesis has been poorly described, and only very recently few examples using this procedure have arised.

Herein, in the course of a project involving synthesis and biological activity of a series of 1,2,3-triazoles, we have expanded our investigation to obtain new \(N\)-substituted phthalimidoalkyl 1H-1,2,3-triazole derivatives. To achieve this goal, we employed a methodology based on click chemistry under ultrasound irradiation, which was more efficient in promoting faster reaction in good yields.
Results and Discussion

In our continuous effort to find new reaction conditions, we applied ultrasound energy in our previously related procedure to prepare 1,2,3-triazole phthalimides via 1,3-dipolar cycloaddition. We described the synthesis of benzoheterocycle-1,2,3-triazole-phthalimides (BTP) from phthalimidopropyl-azide or phthalimidobutyl-azide at conventional condition (CH₂Cl₂/CuI in absence of base or ligand); the reaction occurred within 24 h in moderate-to-good yields of 55-84% (Figure 1).

When we changed to phthalimidoethyl-azide (A₂), we observed lower yields of 33% after 24 h of reaction to afford compound 2a (Table 1, entry 1). Then, the reaction was performed under ultrasound irradiation and the reaction time decreased to 3 h, but no increased yields were observed (entry 1). Furthermore, we broadened our options using phthalimidopropyl-azide (A₃) or phthalimidobutyl-azide (A₄) as substrates, and yet non-homogeneous results were found (Table 1, entries 2-5).

Now, in order to improve our results (yields and reaction time), we focused our endeavor on using a polar solvent, namely acetonitrile. Albeit our effort, we observed a wide yield range between 15-92% in 14-24 h at stirring conditions and room temperature (30 oC) (Table 1, entries 7-10, silent condition). On the other hand, when ultrasound irradiation was applied at short times (1-1.5 h), some results were improved (entries 8 and 9), but the reactions showed a wide yield range (40 to 90%, Table 1, entries 6-10, ultrasound condition). The literature describes that CH₃CN has a high affinity for copper-(I) and therefore can inhibit the reaction, requiring the addition of an amine as ligand. Thus, when we carried out an experiment using CH₃CN, CuI, Ultrasound and Et₃N (Method C) over 2 h to prepare 3b, we observed only 36% of 3b after column chromatography.

Our methodologies (Method A, B and C), so far, showed variable results even after ultrasound irradiation. As an attempt to reach more consistent results, we replaced MeCN by DMF, as a solvent with high dielectric constant.

![Figure 1. Synthesis of benzoheterocycle-1,2,3-triazole-phthalimides (BTP) (adapted from reference 3).](image)

**Table 1. Experiments using methods A and B at silent and ultrasound conditions**

<table>
<thead>
<tr>
<th>Products</th>
<th>entry</th>
<th>Method A: CH₂Cl₂/CuI</th>
<th></th>
<th></th>
<th>Method B: CH₃CN/CuI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Silent (A-S)</td>
<td>Ultrasound (A-US)</td>
<td></td>
<td>Silent (B-S)</td>
<td>Ultrasound (B-US)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>time / h</td>
<td>Yields/ %</td>
<td>time / h</td>
<td>Yields/ %</td>
<td>time / h</td>
<td>Yields/ %</td>
<td>time / h</td>
</tr>
<tr>
<td>2a</td>
<td>1</td>
<td>24</td>
<td>33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3</td>
<td>22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6</td>
<td>NI</td>
</tr>
<tr>
<td>3a</td>
<td>2</td>
<td>28</td>
<td>55&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>95</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>3b</td>
<td>3</td>
<td>24</td>
<td>82</td>
<td>1</td>
<td>89</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>4a</td>
<td>4</td>
<td>22</td>
<td>68&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>4b</td>
<td>5</td>
<td>14</td>
<td>45</td>
<td>3</td>
<td>89</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields after column chromatography; <sup>b</sup>data from reference 3; <sup>c</sup>NI = not investigated; <sup>d</sup>starting material was observed.
We studied the reaction between (A3) and (b) to afford compound 3b and the results are summarized in Table 2.

We found that using only DMF, compound 3b was obtained in 70% yield after 20 h of reaction, with some variation in our template reaction (Table 2, entry 1). In order to accelerate the reaction, we applied ultrasound irradiation and the reactions proceed in 2 h to yield 35% of 3b and the starting material was recovered in 28% (entry 2). When we used DMF and added 10 mol% of Et₃N, the reaction occurred after 25 min in a moderate yield of 58% (entry 3).

As a step forward to improving our methodology, we evaluated the reaction under ultrasound conditions in 30 min to afford 3b in 67% yield (entry 4). With these experiments, we concluded that the independent use of DMF and ultrasound (entry 2) or DMF and Et₃N (entry 3) has not sufficiently improved the results. To rationalize this fact, we believe in a synergistic effect between basic catalyst Et₃N and ultrasound energy, contributed to more optimized conditions (Table 2, entry 4).

Based on these preliminary studies, we adopted the best condition, combining good yields and shorter reaction time. At first, our interests were focused on alkynes bearing the reactive functional groups ethyl propyolate (b), alcohol (c) and ethyl-bromide (d). The reaction proceeded in only 30 min showing more homogeneous results between 67 and 98% yields (Scheme 1 and Table 3, entries 2-4).

In order to investigate the synthesis of other structural scaffolds, we applied our methodology to the synthesis of 4-(2-aminomethyl-1,4-naphthoquinone)-1-(N-phthalimidoalkyl)-1,2,3-triazoles (1e-4e) from 2-(2-propyn-1-yl-amino)-1,4-naphthoquinone (e) and N-phthalimidoalkyl-azides (A1-A4) (Table 3, entry 5).

We started employing our previous conditions used for the synthesis of 2-(1H-1,2,3-triazole)-1,4-naphthoquinone derivatives.¹⁰ The use of CH₃CN and CuI at room

**Table 2. Experiments to synthesis of 3b using DMF as solvent**

<table>
<thead>
<tr>
<th>entry</th>
<th>Condition</th>
<th>time / min</th>
<th>Yields a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>1200</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>DMF/ultrasound</td>
<td>120</td>
<td>35b</td>
</tr>
<tr>
<td>3</td>
<td>DMF/Et₃N</td>
<td>25</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>DMF/Et₃N/ultrasound</td>
<td>30</td>
<td>67</td>
</tr>
</tbody>
</table>

*Yields after column chromatography; b* starting materials were recovered.

**Scheme 1. Synthesis of the 1,2,3-triazoles (1a-e)(4a-e).**
Table 3. Synthesis of N-substituted phthalimidoalkyl 1H-1,2,3-triazoles

<table>
<thead>
<tr>
<th>entry</th>
<th>alkynes (R) (a-e)</th>
<th>Yields / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a = [structure]</td>
<td>41&lt;sup&gt;a&lt;/sup&gt; 33&lt;sup&gt;b&lt;/sup&gt; 55&lt;sup&gt;ab&lt;/sup&gt; 68&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>b = [structure]</td>
<td>93 78 67 83</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>c = [structure]</td>
<td>98 83 88 91</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>d = [structure]</td>
<td>89 68 87 92</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>e = [structure]</td>
<td>96 (20 h)&lt;sup&gt;f&lt;/sup&gt; 60 (19 h)&lt;sup&gt;f&lt;/sup&gt; 79&lt;sup&gt;g&lt;/sup&gt; 91&lt;sup&gt;hd&lt;/sup&gt; 54 (22 h)&lt;sup&gt;e&lt;/sup&gt; 92&lt;sup&gt;de&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>These compounds were obtained using CH<sub>2</sub>Cl<sub>2</sub>/CuI (method A-S); <sup>b</sup>data from literature<sup>3</sup> (method A-S); <sup>c</sup>CH<sub>3</sub>CN/CuI/r.t (method B-S); <sup>d</sup>method D: DMF/Et<sub>3</sub>N/CuI/ultrasound/30 min. |
Conclusions

We have developed a practical and efficient click procedure for the preparation of a molecular library of 18 new N-phthalimidoalkyl 1H-1,2,3-triazoles (1-4) in good-to-excellent yields. The best results were obtained using DMF, CuI and Et₃N under ultrasound irradiation during 30 min at room temperature. Ultrasound irradiation combined with click chemistry promoted the synthesis of a variety of functional groups containing a branched-chain phthalimide linked to 1,2,3-triazole, and this can be a starting point for drug designing through different scaffolds.

Supplementary Information

Supplementary information (spectral data and Figures containing ¹H and ¹³C NMR) is available, free of charge, at http://jbcs.sbq.org.br as a PDF file.

Acknowledgments

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