A New Direct Synthesis of Derivatives of the s-Triazolo[1,5-alpyridine Ring System

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The 1,2,4-triazole nucleus has recently been incorporated into a wide variety of therapeutically interesting drug candidates. We now describe a new synthesis of derivatives of the s-triazolo[1,5-alpyridine system, which contain the 1,2,4-triazole moiety.

s-Triazolo[1,5-alpyridines have been synthesized by the following methods: (a) from 2-aminopyridine by reaction with dimethylformamide dimethyl acetal, followed by treatment either with hydroxylamine-O-sulfonic acid or hydroxylamine and further cyclization by thermal, photochemical, or acidic treatment. The reaction of 2-aminopyridines with aliphatic, aromatic, and heteroaromatic nitriles in the presence of aluminium trichloride leads to N-(2-pyridyl)-alkyl-(or aryl)-amidines, which undergo ring closure to pyrazolo[1,5-alpyridines. Hydroxylamine-O-sulfonic acid reacts with 2-aminopyridine to give 1,2-diaminopyridinium salts which undergo cyclization by reaction with aliphatic and aromatic acids or their chlorides. N-1iminopyridines react with N-ethoxycarbonylimidates to give N-imidoyliminopyridinium ylids which undergo 1,5-dipolar cyclization followed by aromatization to give pyrazolo[1,5-alpyridines.

We report a convenient one-step synthesis of 2-substituted 5,7-diphenyl-s-triazolo[1,5-alpyridines by reaction of 1-amino-
no 4,6-diphenyl-2-pyridone (1), readily available from 4,6-diphenyl-2-pyrene and hydrazine hydrate\textsuperscript{14}, with aromatic and heteroaromatic nitriles 2 under basic conditions.

\[
\begin{array}{c}
\text{C}_6\text{H}_5\text{N} \quad \text{KOC}_{\text{t}-\text{Bu}}\quad \text{t}-\text{C}_6\text{H}_5\text{OH} \\
\text{C}_6\text{H}_5\text{N} \quad \text{C}_6\text{H}_5\text{N} \quad \text{Ar}\to\text{CN} \\
\text{C}_6\text{H}_5\text{N} \quad \text{C}_6\text{H}_5\text{N} \quad \text{Ar}
\end{array}
\]

The best results are obtained when the reaction is carried out in the presence of potassium \textit{t}-butoxide with \textit{t}-butanol as solvent. Attempts with weaker bases such as triethylamine and sodium methoxide were unsuccessful. When treated with one equivalent of potassium \textit{t}-butoxide and one equivalent of nitrile 2 in \textit{t}-butanol under reflux, the N-aminoheterocycle 1 is directly converted to the corresponding \textit{s}-triazolo[1,5-\textit{a}]pyridine 3 in good yield. Furthermore, product isolation is easily accomplished by removal of the solvent and recrystallization of the crude \textit{s}-triazolo[1,5-\textit{a}]pyridines. Structural elucidation of 3 was accomplished on the basis of spectral data and microanalysis.

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**Table.** Preparation of \textit{2-Substituted 5,7-Diphenyl-s-triazolo[1,5-\textit{a}]pyridines 3**

<table>
<thead>
<tr>
<th>Product No.</th>
<th>Ar</th>
<th>Reaction time [h]</th>
<th>Yield\textsuperscript{a} [%]</th>
<th>m.p.\textsuperscript{b} [°C]</th>
<th>Crystallization solvent</th>
<th>Crystal form</th>
<th>Molecular formula \textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>36</td>
<td>72</td>
<td>134-136\textsuperscript{a}</td>
<td>C\textsubscript{6}H\textsubscript{5}OH</td>
<td>Prism</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{3} (347.4)</td>
</tr>
<tr>
<td>3b</td>
<td>4-H\textsubscript{2}C-C\textsubscript{6}H\textsubscript{5}</td>
<td>31</td>
<td>74</td>
<td>158-160\textsuperscript{a}</td>
<td>C\textsubscript{6}H\textsubscript{5}OH</td>
<td>Prism</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{3} (361.5)</td>
</tr>
<tr>
<td>3c</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{5}</td>
<td>24</td>
<td>79</td>
<td>165-167\textsuperscript{a}</td>
<td>CHCl\textsubscript{3}C\textsubscript{6}H\textsubscript{5}OH (1:1, v/v)</td>
<td>Prism</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{3}(Cl\textsubscript{1}) (381.8)</td>
</tr>
<tr>
<td>3d</td>
<td>4-O\textsubscript{2}N-C\textsubscript{6}H\textsubscript{5}</td>
<td>12</td>
<td>70</td>
<td>244-246\textsuperscript{a}</td>
<td>CHCl\textsubscript{3}C\textsubscript{6}H\textsubscript{5}OH (1:1, v/v)</td>
<td>Plates</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}O\textsubscript{2} (392.4)</td>
</tr>
<tr>
<td>3e</td>
<td>4-H\textsubscript{2}CO-C\textsubscript{6}H\textsubscript{5}</td>
<td>24</td>
<td>75</td>
<td>133-136\textsuperscript{a}</td>
<td>C\textsubscript{6}H\textsubscript{5}OH</td>
<td>Prism</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}O (377.4)</td>
</tr>
<tr>
<td>3f</td>
<td>2-pyridyl</td>
<td>24</td>
<td>64</td>
<td>180-181\textsuperscript{a}</td>
<td>CHCl\textsubscript{3}C\textsubscript{6}H\textsubscript{5}OH (1:1, v/v)</td>
<td>Needles</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{2} (348.4)</td>
</tr>
<tr>
<td>3g</td>
<td>4-pyridyl</td>
<td>24</td>
<td>71</td>
<td>185-186\textsuperscript{a}</td>
<td>CHCl\textsubscript{3}C\textsubscript{6}H\textsubscript{5}OH (1:1, v/v)</td>
<td>Needles</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{2} (348.4)</td>
</tr>
<tr>
<td>3h</td>
<td>2-furyl</td>
<td>24</td>
<td>68</td>
<td>151-153\textsuperscript{a}</td>
<td>CHCl\textsubscript{3}C\textsubscript{6}H\textsubscript{5}OH (1:1, v/v)</td>
<td>Needles</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}O (337.4)</td>
</tr>
<tr>
<td>3i</td>
<td>2-thiophen</td>
<td>24</td>
<td>70</td>
<td>138-140\textsuperscript{a}</td>
<td>CHCl\textsubscript{3}C\textsubscript{6}H\textsubscript{5}OH (1:1, v/v)</td>
<td>Needles</td>
<td>C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}S (355.4)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Recrystallized pure product.
\textsuperscript{b} Uncorrected.

The microanalyses were in good agreement with the calculated values: C ±0.27, H ±0.23, N ±0.25.

We have also found that compound 1 reacts with ethyl benzimidates under similar conditions to give 3 in moderate yields (40-50%).

We believe that the mechanism of this reaction involves addition of the N-amino group to the C\textsubscript{==N}-triple bond to give the not isolated intermediate \textit{N}-heteroarylamidine which undergoes cyclocondensation to give 3.

The method appears to be quite general for the aromatic and heteroaromatic series. Yields are high both when the aromatic ring is substituted by electron-donating and electron-withdrawing groups. However attempts with functionally substituted aliphatic and unsaturated nitriles failed to give 3.

The principal advantages of the procedure described here are the high yields, the one-step procedure, the convenient work-up of the products, and the availability of starting materials. Principal disadvantages are slow reaction rates and the applicability to aromatic and heteroaromatic nitriles only.

2-Substituted 5,7-Diphenyl-s-triazolo[1,5-\textit{a}]pyridines 3; General Procedure:

To a solution of 1-amino-4,6-diphenyl-2-pyridone (1: 1.31 g, 5 mmol) in \textit{t}-butanol (50 ml), potassium \textit{t}-butoxide (0.56 g, 5 mmol) and the appropriate aromatic nitrile 2 (5 mmol) are added. The reaction mixture develops a deep red colour which disappears on heating under reflux for 12-36 h (Table). After cooling the solvent is removed under reduced pressure and the resulting crude product recrystallized from the appropriate solvent.

\begin{thebibliography}{99}
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