SYNTHESIS OF TETRAPHENYL-FUROINDOLES VIA TANDEM REACTIONS

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Abstract – We report a novel one-step synthesis of tetraphenyl substituted furoindoles involving acid-catalyzed cascade approach of commercially available m-aminophenols with readily accessible α-hydroxyaldehydes. The tandem reactions involved nucleophilic addition, aldimine condensation, pinacol rearrangement, α-iminol rearrangement, cyclization and dehydration aromatization process. The yield of furoindoles was up to 75%.

Tetraphenyl substituted furoindoles are crucial structural motifs in various organic materials.¹ As a result, the synthesis of these target molecules by feasible methodologies have great significance, and indeed, various synthetic routes have been used for the construction of tetraphenyl substituted furoindoles and their derivatives. Some of synthetic strategies toward tetraphenyl substituted furoindoles are shown in Scheme 1. The classic method for the synthesis of tetraphenyl substituted furoindoles involves Pd catalyzed condensation of halogenated arenes with phenylacetylene (path a, Scheme 1).¹b Unfortunately, this method needs 4 steps to give access to tetraphenyl substituted furoindoles. Another method only needs two steps to give access to tetraphenyl substituted furoindoles, but this approach needs special phosphorus ligand (path b and c Scheme 1).¹c,¹f In 2018, Yan group introduced one approach for the p-toluenesulfonic acid (PTSA) catalyzed synthesis of tetraphenyl substituted furoindoles. The yield of this approach can only reach to 35% showing only one example (path d, Scheme 1).¹e Sahoo developed a novel synthesis of tetraphenyl substituted furoindoles involving Pd and Rh catalyzed oxidative annulations of both commercially available phenols with diphenylacetylene. This method can synthesize two types of tetraphenyl substituted furoindoles. The yield can reach to 36% (over 2 steps) and 29% (over 3 steps), and there are only two products in the literature (path e, Scheme 1).¹g The α-iminol
The rearrangement reaction was first reported in 1943.\textsuperscript{2} α-Iminol rearrangement is an efficient method for the preparation of α-amino ketones from α-hydroxy imines. α-Iminol rearrangement involves the shift of a substituent of the adjacent carbon to the imine carbon. The rearrangement can also be conducted on imines generated in situ from carbonyl compounds and amines.\textsuperscript{3} The acid catalyzed conversion of pinacols to carbonyl compounds through dehydration and subsequent 1,2-migration is a valuable reaction known as the pinacol rearrangement.\textsuperscript{4,5} We wish to report a method for the synthesis of the tetraphenyl substituted furoindoles, which is featuring one-step synthesis of tetraphenyl substituted furoindole moiety and distinctly different from all previous approaches (path f, Scheme 1).\textsuperscript{1}

Previous work  Synthesis of tetraphenyl-furoindoles via step by step reactions

\begin{align*}
\text{(a)} & \quad \begin{array}{c}
\text{Br} \\
\text{O}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \xrightarrow{\text{Pd/L}} \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\end{align*}

\begin{align*}
\text{(b)} & \quad \begin{array}{c}
\text{Br} \\
\text{O}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \xrightarrow{\text{Pd/L}} \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\end{align*}

\begin{align*}
\text{(c)} & \quad \begin{array}{c}
\text{Br} \\
\text{O}
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \xrightarrow{\text{Pd/L}} \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\end{align*}

\begin{align*}
\text{(d)} & \quad \begin{array}{c}
\text{OH} \\
\text{NH}_{2}
\end{array} \xrightarrow{\text{120 mol\% PTSA}} \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{align*}

\begin{align*}
\text{(e)} & \quad \begin{array}{c}
\text{OH} \\
\text{NHAc}
\end{array} \xrightarrow{\text{diphenylacetylene}} \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{align*}

Our work  Synthesis of tetraphenyl-furoindoles by Cascade reactions

\begin{align*}
\text{(f)} & \quad \begin{array}{c}
\text{OH} \\
\text{NH}_{2}
\end{array} + \begin{array}{c}
\text{OH}
\end{array} \xrightarrow{\text{TsOH/H}_{2}\text{O}} \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{align*}

Scheme 1. Strategies toward tetraphenyl substituted furoindoles
The synthetic study firstly commenced with the substrate 1a, which is commercially available, and readily accessible α-hydroxyaldehyde 2 using TsOH·H₂O (40 mol%) as the catalyst in toluene solvent. The results in Table 1 showed that increase reaction temperature reasonably could promote this reaction (entries 1-3). The reaction temperature must be increased slowly in order to reduce side reactions. The relative strength of acid has an important impact on this reaction. The stronger acid could promote this reaction (entries 2, 4). The results in Table 1 showed that desiccant was unfavorable to this reaction (entries 5-6). After being optimized, the yield of 3a can reached to 53%.

**Table 1.** Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>T (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsOH·H₂O</td>
<td>-</td>
<td>110</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>TsOH·H₂O</td>
<td>-</td>
<td>130</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>TsOH·H₂O</td>
<td>-</td>
<td>150</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>PPTS</td>
<td>-</td>
<td>130</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>TsOH·H₂O</td>
<td>4 Å M.S.</td>
<td>130</td>
<td>n.d.&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>TsOH·H₂O</td>
<td>MgSO₄</td>
<td>130</td>
<td>11</td>
</tr>
</tbody>
</table>

Reaction conditions: 1a (0.1 mmol); 2 (0.24 mmol, 1.2 eq); catalyst (0.4 eq); additive (100 mg); reaction temperature: 25 °C (1.5 h); 60 °C (1.5 h); 80 °C (1 h); 100 °C (1 h); T (°C) (90 h); under a nitrogen atmosphere; toluene (2 mL). <sup>a</sup> Isolated yield. <sup>b</sup> n.d. = not detected.

With the optimal reaction conditions in hand, we next turned our attention to the scope and functional group tolerance of this transformation. Scheme 2 summarizes the annulation of various m-aminophenols 1 with 2. The results in Scheme 2 showed that steric hindrance and substituent properties both have important impact on this reaction. When the substituents are the same (Me, Br), as 1,3,4-trisubstituted m-aminophenols have smaller steric hindrance than 1,2,3-trisubstituted m-aminophenols, so 3b and 3d have higher yields than 3a and 3c, respectively (3b>3a, 3d>3c). Both as 1,3,4-trisubstituted or 1,2,3-trisubstituted, electron-donating substituents have higher yields than electron-withdrawing substituents (3a>3c, 3b>3d, 3e, 3f).
Scheme 2. Synthesis of 3 by Tandem reactions. Reaction conditions: 1 (0.1 mmol); 2 (0.24 mmol, 1.2 eq); TsOH·H$_2$O (0.4 eq); reaction temperature: 25 °C (1.5 h); 60 °C (1.5 h); 80 °C (1 h); 100 °C (1 h); 130 °C (90 h); under an nitrogen atmosphere; toluene (2 mL). Yields of isolated product are given.

A plausible mechanism is outlined in Scheme 3. Substrates 1a and 2 were converted into intermediate D through aldimine condensation, α-iminol rearrangement, cyclization and dehydration-aromatization process in the presence of TsOH·H$_2$O. Then, intermediate D underwent nucleophilic addition, pinacol rearrangement, cyclization and dehydration-aromatization process to form 3a.
In conclusion, we developed a novel organocatalytic method to access tetraphenyl substituted furoindoles via one-pot reaction. According to this metal-free methodology, a range of highly substituted tetraphenyl substituted furoindoles were synthesized. The fused ring systems contain a tetraphenyl substituted furoindoles which had shown their potential as organic photoelectric materials. The applications of tetraphenyl substituted furoindoles and further detailed mechanistic studies are currently in progress in our laboratory.

ACKNOWLEDGEMENTS
Financial support from the Natural Science Foundation of Jiangsu Province (BK20191197) is gratefully acknowledged.

SUPPORTING INFORMATION
Supplementary data (Experimental procedures and details, Characterization data for products, NMR spectra for all products) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27257/102/8.

REFERENCES AND NOTES


