A Streamlined Synthesis of 2,3-Dihydrobenzofurans via the ortho-Quinone Methides Generated from 2-Alkyl-Substituted Phenols

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Abstract: A facile method for the stereoselective synthesis of trans-2,3-dihydrobenzofurans from ortho-quinone methides in situ generated from readily available 2-alkyl-substituted phenols using silver oxide-mediated oxidation has been developed. Additionally, the 2,3-dihydrobenzofurans can be further transformed into the aromatized 2,3-disubstituted benzofurans in the presence of DDQ.

Keywords: 2,3-dihydrobenzofurans; ortho-quinone methides; synthesis

2,3-Dihydrobenzofuran derivatives are an important class of compounds due to their remarkable significance in various biological active molecules, synthetic drugs and natural products. For instance, (+)-conocarpan which was first isolated from the wood of Conocarpus erectus acts as an insecticidal, antifungal and antitrypanosomal agent. Obtusafuran is a quinone reductase and propafenone-derived dihydrobenzofurans possess anti-multidrug resistance properties (Figure 1). Additionally, 2,3-dihydrobenzofurans have also been developed for the treatment of traumatic and ischemic central nervous system injury. Thus, the synthesis of 2,3-dihydrobenzofurans has received extensive attention in the past decades and various efficient methodologies for the construction of 2,3-dihydrobenzofurans have been developed, including electrocyclization, radical cyclization, anionic cyclization, transition metal-catalyzed cyclization, cycloaddition, biomimetic coupling, Lewis acid-promoted reactions. Although significant progress has been made in the synthesis of 2,3-dihydrobenzofurans, most of these existing routes have several drawbacks involving poor chemo- and/or diastereoselectivities, unsatisfactory yields, tedious processes and harsh reaction conditions, prohibiting their wider application. Therefore, the development of a convenient, efficient and atom-economical method for the rapid synthesis of these derivatives is still highly desirable.

ortho-Quinone methides (o-QMs) are emerging as versatile intermediates in a large number of chemical and biological processes. Consequently, several approaches have been successfully developed for generating o-QMs, including tautomerization, oxidation, acid or base catalysis, thermolysis, photolysis and olefination of o-quinones which have been described in the literature. Recently, we reported an efficient approach for the generation of o-QMs intermediates under the mild basic conditions which further underwent reaction with sulfur ylides to afford the trans-2,3-dihydrobenzofurans with high yields (Scheme 1). Considering that the o-QMs intermediates could be conveniently generated by the oxidation of easily available 2-alkyl-substituted phenol derivatives, we speculated that the generated o-QMs intermediates could berapidly trapped by sulfur ylides to allow the construction of 2,3-dihydrobenzo-
furans, which is more atom-economical and simple in comparison to our previous work. Herein, we disclose a straightforward and atom-economical method for the rapid synthesis of 2,3-dihydrobenzofurans via the o-QMs generated from 2-alkyl-substituted phenols in the presence of an oxidant (Scheme 1).

Our initial investigation was conducted with 2-alkyl-substituted phenol 1a (1.2 equiv) and sulfonium salt 2a as model substrates at room temperature. The oxidant played a crucial role in the reaction and triggered the generation of o-QMs intermediates, therefore the oxidant was firstly thoroughly evaluated.

To our delight, the reaction proceeded smoothly to provide the desired product 3a in 92% yield and excellent diastereomeric ratio when Ag2CO3 was employed as oxidant (entry 1, Table 1). However, the other oxidants, AgNO3, DDQ, BPO and PhI(OAc)2, displayed lower reactivity (entries 2–5) and K3[Fe(CN)6] gave only moderate yields albeit with perfect diastereoselectivity (entry 6). Additionally, good yields and diastereoselectivity were also obtained in the presence of Ag2O as oxidant (entry 7). Subsequently, different solvents were extensively examined, and it was found that the solvent effect displayed a significant influence on the reactivity (entries 8–12). CH2Cl2 was proven to be the most favorable solvent with respect to excellent yields and diastereoselectivity. Finally, the influence of base was explored. Several common anionic bases, such as Na2CO3, NaOH, KO-t-Bu and K2CO3, all afforded the desired product in satisfactory yields (entries 12–17). For the reason that K2CO3 is cheaper and easy to handle it was chosen as the best base.

Scheme 1. The new strategy for the synthesis of 2,3-dihydrobenzofurans.

Table 1. Optimization for the reaction of 2-alkyl-substituted phenol 1a with sulfonium salt 2a.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Oxidant</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>Ag2CO3</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>AgNO3</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>DDQ</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>BPO</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>PhI(OAc)2</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>K3[Fe(CN)6]</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>CH2Cl2</td>
<td>Cs2CO3</td>
<td>Ag2O</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>Et2O</td>
<td>Cs2CO3</td>
<td>Ag2O</td>
<td>55</td>
</tr>
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<td>THF</td>
<td>Cs2CO3</td>
<td>Ag2O</td>
<td>71</td>
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<td>10</td>
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<td>Cs2CO3</td>
<td>Ag2O</td>
<td>45</td>
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<td>11</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>Ag2O</td>
<td>11</td>
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<td>12</td>
<td>EtOH</td>
<td>Cs2CO3</td>
<td>Ag2O</td>
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<td>Na2CO3</td>
<td>Ag2O</td>
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<tr>
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<td>CH2Cl2</td>
<td>NaOH</td>
<td>Ag2O</td>
<td>91</td>
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<td>Ag2O</td>
<td>88</td>
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<tr>
<td>16</td>
<td>CH2Cl2</td>
<td>KO-t-Bu</td>
<td>Ag2O</td>
<td>97</td>
</tr>
<tr>
<td>17</td>
<td>CH2Cl2</td>
<td>K2CO3</td>
<td>Ag2O</td>
<td>95</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.24 mmol), 2a (0.20 mmol), base (1.2 equiv.), oxidant (2.0 equiv.), solvent (3 mL), room temperature, 12 h. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; BPO = benzyol peroxide.

[b] Isolated yields.
With the aforementioned reaction conditions in hand, we explored the reaction scope using a variety of 2-alkyl-substituted phenols 1 and sulfonium salts 2 (Scheme 2). In general, the transformations performed very well and moderate to excellent yields were obtained. Notably, for aryl substituents R\textsuperscript{1}, the electronic property had little influence on the yield and diastereoselectivity. For example, the reactions furnished the desired product 3\textbf{a} and 3\textbf{e} in the 95% and 89% yield, respectively. Interestingly, vinyl substrate 1\textbf{g} was a suitable reaction partner and provided the product in the good yield which could then be applied to further transformations. Nevertheless, replacement of substrate 1\textbf{a} by 4,5-dimethoxy-2-(4-methoxyphenyl)-6,7-dihydrobenzofuro[6,5-\textit{d}][1,3]dioxole-6-carboxamide 3\textbf{l}, see the Supporting Information. \cite{17}

The product 2,3-dihydrobenzofurans could be further converted into the corresponding aromatic benzofurans, which is a privileged scaffold in various important natural products and show a wide range of biological activities.\cite{18} Using DDQ as the oxidizing agent, 2,3-dihydrobenzofuran products 3\textbf{a} and 3\textbf{b} can be transformed smoothly to the desired aromatized products 4\textbf{a} and 4\textbf{b} with good yields according to the known literature method (Scheme 3).\cite{19}

In conclusion, we have developed a facile method for the synthesis of 2,3-dihydrobenzofurans via the o-QMs in situ generated from readily available 2-alkyl-substituted phenols using silver oxide-mediated oxidation in good yields and excellent diastereoselectivity. In addition, 2,3-dihydrobenzofurans were conveniently converted to the aromatized 2,3-disubstituted benzofurans using DDQ as oxidant.

**Experimental Section**

**General Procedure for the Synthesis of 2,3-Dihydrobenzofurans**

A reaction mixture of 2-alkyl-substituted phenol 1 (0.24 mmol), sulfonium salt 2 (0.20 mmol), Ag\textsubscript{2}O (111 mg, 0.48 mmol) and K\textsubscript{2}CO\textsubscript{3} (33 mg, 0.24 mmol) in dichloromethane (3 mL) was stirred at room temperature for 12 h. Then water (20 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 mL) and the combined organic layer was dried by anhydrous sodium sulfate, concentrated...
under vacuum. The crude product was purified by flash chromatography on silica gel using petroleum ether and ethyl acetate to give the corresponding trans-2,3-dihydrobenzofuran products 3.

trans-7-(4-Methoxyphenyl)-6,7-dihydrobenzofuro[6,5-d]-[1,3]dioxol-6-yl[phenyl]methanone (3a): yield: 95%; 1H NMR (400 MHz, CDCl3): δ = 7.97–7.87 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.65 (s, 1H), 6.42 (s, 1H), 5.94–5.85 (m, 2H), 5.76 (d, J = 6.2 Hz, 1H), 3.81 (s, 3H); 13C NMR (100 MHz, CDCl3): δ = 195.0, 159.2, 153.8, 153.8, 148.2, 142.7, 134.6, 134.0, 129.4, 129.2, 128.9, 120.6, 114.5, 105.2, 101.6, 93.4, 91.7, 55.5, 50.6; HR-MS: m/z = 397.1031, calculated for C17H13NO3 [M+Na]+: 397.1052.

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References

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COMMUNICATIONS


[17] CCDC 945017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
