An unexpected aromatization reaction during the preparation of 1,2-cyclohexanediene ethers

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Abstract: In a heretofore-unreported reaction, 1,2-cyclohexanediene reacts with a variety of alcohols under mild acid-catalyzed dehydration conditions to afford not only ethers of 1,2-cyclohexanediene but the corresponding aryl ethers as well in moderate to good yield.

Keywords: 1,2-cyclohexanediene; aromatization; aryl ethers. © 2017 ACG Publications. All rights reserved.

1. Introduction

During the course of a synthetic methods investigation, we required the preparation of the diosphenol ether 3 from the reaction of o-bromobenzyl alcohol (1) and 1,2-cyclohexanediene (2) in accordance to a literature procedure (Scheme 1).\(^1\) While the desired product was observed, much to our surprise we isolated the corresponding phenyl ether 4 in significant, albeit low yield. This prompted us to investigate the reaction of a variety of alcohols with 1,2-cyclohexanediene under acidic conditions.

\[
\begin{align*}
\text{Br} & \quad \text{O} \quad \text{O} \\
\text{Br} & \quad \text{O} \\
\text{D} & \quad \text{p-TSA/PhCH}_3
\end{align*}
\]

Scheme 1. Acid-catalyzed reaction of o-bromobenzyl alcohol with 1,2-cyclohexanediene

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2. Experimental Section

2.1. Chemicals
1,2-Cyclohexanedione was purchased from Ontario Chemicals and was used as received. Other chemicals were purchased from Sigma-Aldrich Chemicals. IR spectra were recorded on a Perkin-Elmer Spectrum Two Fourier Transform Infrared Spectrometers. \(^1\)H (400 MHz) and \(^{13}\)C (100 MHz) NMR were recorded on a Bruker Biospin Ascend 400 MHz Nuclear Magnetic Resonance Spectrometer using CDCl\(_3\) as solvent and TMS as an internal standard. Silica gel flash column chromatography was performed using E. Merck silica gel (230-400) and E. Merck TLC plates. Low resolution mass spectrometry was performed on a Agilent 6890 Gas Chromatograph/5973 Quadrupole Mass Spectrometer System at 70 eV with a 7683B Autoinjector. The high-resolution mass spectrum was obtained on an Agilent LCTOF.

2.2 General method for the preparation of aryl ethers: Compounds 4a-d and 4g-j were synthesized by the method detailed below and their structural assignment confirmed by comparison of spectral data to that reported in the literature.

Preparation of 1,2-dimethoxy-4-(2-phenoxyethyl)benzene (4e): To a 250 mL round bottom flask equipped with a Dean-Stark tube and reflux condenser was added 1,2-cyclohexanedione (1.12 g; 10 mmol) dissolved in toluene (100 mL). 3,4 Dimethoxy-β-phenylethyl alcohol (2.28 g; 12.5 mmol) was then added to the flask, followed by the addition of p-TSA (170 mg; 0.98 mmol). The reaction mixture was refluxed for 24 h. The reaction was cooled to 0°C, and an additional 125 mL of toluene was added. The mixture washed with 100 mL of 0.5 M Na\(_2\)CO\(_3\). The organic layer was separated and washed with additional 0.5 M Na\(_2\)CO\(_3\) (2 x 200 mL). The organics were then dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 98:2 hexanes/EtOAc to afford a 4e as clear colorless viscous oil: (697 mg; 27%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.27-7.15 (m, 7H), 6.90-6.82 (m, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.20 (t, \(J = 7.2\) Hz, 2H), 3.08 (t, \(J = 7.2\)Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) (100 MHz, CDCl\(_3\)) \(\delta\) 158.8, 149.1, 147.7, 131.1, 129.5, 120.9, 120.8, 114.6, 112.5, 111.4, 68.9, 56.0, 55.9, 35.6. HRMS for C\(_{16}\)H\(_{18}\)O\(_3\): calc’d \(m/z\): 258.1256; found \(m/z\): 258.1261.

3. Results and Discussion

Using a variety of aryl substituted alcohols, we found that in each case a substantial amount of aryl ether product along with the expected dione ether was formed and in several cases, the aryl ethers were the major product (1e, 1g-1i). We found this interesting in light of the work of Kablaoui who has described the aromatization of 1,2-, 1,3-, and 1,4-cyclohexanediones using forcing conditions employing a strong acid/Ac\(_2\)O/AcOH system (Scheme 2) to afford pyrocatechol, resorcinol, and hydroquinone after hydrolysis of the corresponding O-acylated derivatives,\(^2\) while Feigenbaum, et al. have described the conversion of 3-aryl-1,2-cyclohexanediol to the corresponding catechols using a p-toluenesulfonyl chloride/K\(_2\)CO\(_3\)/AIBN system (Scheme 3).\(^3\)

\[ \begin{aligned} \text{O} & \quad \text{Ac}_2\text{O/AcOH/D} \\ 1) \text{H}_2\text{SO}_4 & \quad \text{OH} \\ 2) \text{H}_2\text{O} & \quad \text{OH} \end{aligned} \]

Scheme 2. Aromatization of 1,2-cyclohexanedione to catechol under acidic conditions
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These reaction conditions are far more rigorous compared to those employed in this study. A possible mechanism for aryl ether formation is shown below (Scheme 4).

Scheme 3. Aromatization of 1,2-cyclohexanedione derivatives to catechol under basic conditions

Scheme 4. Proposed mechanism for the aromatization of ethers derived from 1,2-cyclohexandione under acidic conditions

4. Conclusion

1,2-Cyclohexanedione can undergo dehydrative aromatization reactions with alcohols under relatively mild conditions. To the best of our knowledge, this type of mild aromatization reaction with 1,2-cyclohexanedione has not been reported. Future studies will focus on the scope and limitations of this chemistry.
Table 1. Synthesized Compounds

<table>
<thead>
<tr>
<th>ROH</th>
<th>%</th>
<th>%</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a ( \text{Br} )</td>
<td>70</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>1b ( \text{CH}_2\text{OH} )</td>
<td>65</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>1c ( \text{CH}_2\text{OH} )</td>
<td>75</td>
<td>15</td>
<td>4,8</td>
</tr>
<tr>
<td>1d ( \text{H}_3\text{CO} )</td>
<td>73</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>1e ( \text{CH}_2\text{OH} )</td>
<td>8</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td>1f ( \text{OH} )</td>
<td>44</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>1g ( \text{CH}_2\text{OH} )</td>
<td>17</td>
<td>72</td>
<td>11</td>
</tr>
<tr>
<td>1h ( \text{CH}_3\text{O} )</td>
<td>19</td>
<td>71</td>
<td>12,13</td>
</tr>
<tr>
<td>1i ( \text{HO} )</td>
<td>29</td>
<td>70</td>
<td>(a)</td>
</tr>
<tr>
<td>1j ( \text{HO} )</td>
<td>22</td>
<td>34</td>
<td>(b)</td>
</tr>
</tbody>
</table>

*a* based on stoichiometry of 1 mole hydroquinone/1 mole 1,2-cyclohexanediol. The ether product is 4-phenoxyl-phenol.

*b* based on stoichiometry of 1 mole diol/2 moles 1,2-cyclohexanediol

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/OC

References


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