Synthesis of Substituted 2,3,5,6-Tetraarylbenzo[1,2-b:5,4-b']difurans

Mahmoud Abdul-Aziz
Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078

Judith V. Auping and Michael A. Meador
Polymers Branch, Materials Division, NASA Lewis Research Center, Cleveland, Ohio 44135-3191

Reprinted from
J. ORG. CHEM., Volume 60, Number 5, Pages 1303–1308
Synthesis of Substituted 2,3,5,6-Tetraarylenbenzo[1,2-b:5,4-b']difurans

Mahmoud Abdul-Aziz

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078

Judith V. Auping and Michael A. Meador

Polymers Branch, Materials Division, NASA Lewis Research Center, Cleveland, Ohio 44135-3191

Received July 6, 1994

A series of substituted 2,3,5,6-tetraarylenbenzo[1,2-b:5,4-b']difurans 1 was synthesized. This synthesis is based upon the photocyclization of 2,5-dibenzoylresorcinol dibenzyl ethers to the corresponding tetrahydrobenzo[1,2-b:5,4-b']difurans. Treatment of the photoproducts with methanesulfonyl chloride in pyridine afforded 1 in overall yields ranging from 30-72%. A number of these compounds have high fluorescence quantum yields (φF = 0.76–0.90), and their fluorescence spectra exhibit large solvatochromic shifts. These compounds may be suitable for use as fluorescent probes.

Introduction

Intramolecular hydrogen abstractions are among some of the best studied reactions in organic photochemistry. The most prevalent examples of these involve abstraction of a γ-hydrogen, i.e., the Norrish Type II reaction. However, a number of cases of both δ- and ε-hydrogen abstraction have been reported. Higher forms of hydrogen abstraction, such as these, have attracted a fair amount of recent interest, not only because they provide useful insight into ketone photochemistry and biradical behavior, but many have potential synthetic utility in the construction of five- and six-membered rings.

One example of a δ-hydrogen abstraction which has found some applications in synthesis is the photocyclization of o-alkoxyphenyl ketones 2 to 2,3-disubstituted-3-hydroxy-2,3-dihydrobenzofurans 4 (Scheme 1). Irradiation of ketone 2 leads to the formation of a biradical intermediate, 3, via a triplet state intramolecular abstraction of a benzoyloxy hydrogen by the carbonyl oxygen. This biradical intermediate can undergo a 1,5 cyclization to 4 (path A). In some cases, a competing 1,3-cyclization can occur (path B) to produce a spiro-epoxide intermediate, 6, which rearranges to the corresponding 2-acylbenzyl alcohol 7, or its hemiketal, 8.

For o-(benzyl)oxyacetophenone, 2 (R = Ph, R = CH₃), 1,3-cyclization predominates leading to formation of 2-acylbenzyl alcohol. Similar results have been reported for o-(cyclopropylmethoxy)acetophenone, other o-alkoxyacetophenones, and o-alkoxybenzaldehydes.

On the other hand, o-(benzyl)oxybenzophenone, 2 (R, R' = Ph), photocyclizes exclusively (100% yield) to 3-hydroxy-2,3-diphenyl-2,3-dihydrobenzofuran, 4 (R, R' = Ph), with a high quantum efficiency (0.95). Dehydration of the dihydrobenzofuranol photoproduct with HCl produces 2,3-diphenyldifuran, 5 (R, R' = Ph), in 100% yield. High chemical yields have also been reported for the photocyclization of o-(allyloxy)- and o-(propargyloxy)-benzophenones and their subsequent dehydration to substituted benzo[1,2-b:5,4-b']difurans. This photochemistry has also been used in the synthesis of aflatoxin M₁. Thus, this

Scheme 1. Photocyclization of o-Alkoxyphenyl Ketones

![Scheme 1](attachment://Scheme_1.png)

Scheme 2. Synthesis of 1

\[
\begin{align*}
\text{a)} & \quad \text{K}_2\text{CO}_3, \text{K}_2\text{HPO}_4, \text{Bu}_3\text{N} \rightarrow \text{H}_2\text{O}, \text{reflux} \text{N}_2, 18 \text{ h;} \\
\text{b)} & \quad \text{2-CH}=\text{Z}, \text{reflux} \text{N}_2, 18 \text{ h;} \\
\text{c)} & \quad \text{K}_2\text{CO}_3, \text{K}_2\text{HPO}_4, \text{Bu}_3\text{N} \rightarrow \text{H}_2\text{O}, \text{reflux} \text{N}_2, 18 \text{ h;} \\
\text{d)} & \quad \text{2-CH}=\text{Z}, \text{reflux} \text{N}_2, 18 \text{ h;} \\
\text{e)} & \quad \text{MeSO}_2\text{Cl}/\text{pyridine} \\
\end{align*}
\]

(a) 1.) K$_2$CO$_3$, KI, Bu,NHSO$_4$/H$_2$O, reflux N$_2$, 18 h; 
(b) 1.) K$_2$CO$_3$, KI, Bu,NHSO$_4$/H$_2$O, reflux N$_2$, 18 h; 
(c) by/C$_6$H$_5$, N$_2$, Pyrex Filter; (d) MeSO$_2$Cl/pyridine

Method constitutes a simple, high-yield approach to substituted benzo[1,2-b:5,4-b']difurans.

We have been applying this chemistry to the synthesis of highly substituted benzo[1,2-b:5,4-b']difurans and have recently examined this photocyclization in polymers containing o-(benzyloxy)benzoyl chromophores. We have now used this photochemistry in the synthesis of a series of substituted tetraarylbenzo[1,2-b:5,4-b']difurans, 1 (Scheme 2). Through this method, symmetrically and unsymmetrically substituted benzodifurans were prepared, including donor/acceptor substituted systems. We now report the results of these efforts.

Results and Discussion

2,3,5,6-Tetraarylbenzo[1,2-b:5,4-b']difurans 1 were prepared from substituted 1,3-dihydroxy-2,5-dibenzo[b]zenes 9, according to the synthesis outlined in Scheme 2. Symmetrically and unsymmetrically substituted 2,5-diaroylresorcinol dibenzyl ethers 11 were prepared in one or two steps from 9 via a modified Williamson ether synthesis under phase transfer conditions. Yields for the synthesis of 11 are presented in Table 1.

Table 1. Yields for Synthesis of 2,3,5,6-Tetraarylbenzo[1,2-b:5,4-b']difurans 1 and 1,3-Bis(benzyloxy)-4,6-dibenzoylbenzenes 11

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>% yield, 11</th>
<th>% yield, 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>80</td>
<td>69</td>
</tr>
<tr>
<td>b</td>
<td>4-CN</td>
<td>4-CN</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>c</td>
<td>4-MeO</td>
<td>4-MeO</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>d</td>
<td>3,5-(MeO)$_2$</td>
<td>3,5-(MeO)$_2$</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>e</td>
<td>4-CN</td>
<td>4-MeO</td>
<td>49</td>
<td>70</td>
</tr>
<tr>
<td>f</td>
<td>4-CN</td>
<td>3,5-(MeO)$_2$</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>Me</td>
<td>83</td>
<td>68</td>
</tr>
<tr>
<td>h</td>
<td>4-CN</td>
<td>Me</td>
<td>92</td>
<td>76</td>
</tr>
<tr>
<td>i</td>
<td>4-MeO</td>
<td>Me</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>j</td>
<td>3,5-(MeO)$_2$</td>
<td>3,5-(MeO)$_2$</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>k</td>
<td>4-CN</td>
<td>4-MeO</td>
<td>52</td>
<td>61</td>
</tr>
<tr>
<td>l</td>
<td>4-CN</td>
<td>3,5-(MeO)$_2$</td>
<td>53</td>
<td>56</td>
</tr>
</tbody>
</table>

* Formed in two steps from the corresponding monoether (10a or 10b), overall yields from 9 reported first, yields from 10a or 10b are given in parentheses.

Photolysis of ~0.01M benzene solutions of 11 under nitrogen produced the desired 2,6-dihydroxy-2,3,5,6-tetrahydrobenzo[1,2-b:5,4-b']difuran, 12, as a mixture of stereoisomers in quantitative yield. Spectral data are consistent with the formation of the desired products. Competing reactions have been observed in the photocyclization of o-alkoxyacetophenones leading to the formation of o-acylbenzyl alcohols (Scheme 1). Photolysis of 2-(benzyloxy)-4-(dodecyloxy)benzophenone, 13, leads to photocleavage product 17 and benzol[bingenanthro[9,10-d]furin, 16, as well as dihydrobenzofuran, 14 (eq 1). However, $^1$H- and $^{13}$C-NMR reveal no evidence of unreacted starting materials, unwanted side products, or secondary photoproducts in the present systems.

Attempts to convert the photoproducts into the corresponding benzo[1,2-b:5,4-b']difurans through an acid-catalyzed dehydration were unsuccessful. Unlike simple 3-hydroxy-2,3-dihydrobenzofurans, treatment of 12 with a trace amount of HCl in benzene or diethyl ether produced a significant amount of side products. Attempts to use other acids (mineral, organic, or Lewis) either resulted in no dehydration or led to the formation of the same side products.

No attempt was made to isolate and purify these side products. However, $^1$H-NMR of the crude product mix-
Synthesis of 2,3,5,6-Tetraarylbenzo[1,2-b:5,4-b']difurans

Scheme 3. Pinacol Rearrangement of 12

[Chemical structures and reactions described]

To our knowledge only one other synthesis of tetraphenylbenzo[1,2-b:5,4-b']difurans has been reported in the literature. This involved an acid-catalyzed cyclodehydration of resorcinol with p-(benzyloxy)benzoin in refluxing 1,4-dioxane (eq 2). The method that we have described in this paper employs considerably milder conditions than these, with slightly lower overall yields. Overall yields for the preparation of 1 from dibenzoylresorcinols 9 range from 30 to 72%, with the symmetrically substituted derivatives having the highest yields.

Another strength of the present procedure is that it provides a route to donor/acceptor substituted compounds which may have some use as fluorescent probes in biological and polymeric systems. Requirements for these probes are a high fluorescence quantum yield and a sensitivity of the fluorescence spectrum to the polarity of its environment.

Fluorescence quantum yields for 1 in methycyclohexane are quite high, ranging from 0.76 to 0.98 (Table 2). Quantum yields varied slightly with substituents. Donor/acceptor substituted compounds, e.g. 1e and 1f, had the lowest values. Emission spectra of donor/acceptor substituted 1 were measured in solvents of varying polarity (Table 3). Fluorescence emission spectra were red shifted in solvents of increasingly higher polarity. These solvatochromic shifts are large, as much as 100 nm for 1e in methycyclohexane vs DMSO. The photophysics of these compounds is currently under investigation.

Table 2. Fluorescence Data for 1 in Methylcyclohexane

<table>
<thead>
<tr>
<th>I</th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>λmax&lt;sup&gt;c&lt;/sup&gt;</th>
<th>δ&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>387</td>
<td>0.95</td>
</tr>
<tr>
<td>b</td>
<td>4-CN</td>
<td>4-CN</td>
<td>H</td>
<td>407</td>
<td>0.98</td>
</tr>
<tr>
<td>c</td>
<td>4-CN</td>
<td>4-MeO</td>
<td>H</td>
<td>421</td>
<td>0.91</td>
</tr>
<tr>
<td>d</td>
<td>4-CN</td>
<td>3,5-(MeO)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>411</td>
<td>0.88</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>387</td>
<td>0.98</td>
</tr>
<tr>
<td>f</td>
<td>4-CN</td>
<td>4-CN</td>
<td>Me</td>
<td>391</td>
<td>0.92</td>
</tr>
<tr>
<td>g</td>
<td>4-CN</td>
<td>4-MeO</td>
<td>Me</td>
<td>423</td>
<td>0.79</td>
</tr>
<tr>
<td>h</td>
<td>4-CN</td>
<td>3,5-(MeO)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Me</td>
<td>413</td>
<td>0.84</td>
</tr>
</tbody>
</table>

<sup>a</sup> Longest wavelength band, nm. <sup>b</sup> Anthracene used as the actinometer (ϕ <i>s</i> = 0.27).

Table 3. Solvent Dependence of Fluorescence Emission Maxima<sup>c</sup> for 1

<table>
<thead>
<tr>
<th>solvent&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ib</th>
<th>le</th>
<th>If</th>
<th>lh</th>
<th>lk</th>
<th>lI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>495</td>
<td>527</td>
<td>441</td>
<td>451</td>
<td>518</td>
<td>487</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>471</td>
<td>522</td>
<td>427</td>
<td>443</td>
<td>498</td>
<td>478</td>
</tr>
<tr>
<td>1,2-EtCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>452</td>
<td>453</td>
<td>422</td>
<td>423</td>
<td>491</td>
<td>449</td>
</tr>
<tr>
<td>THF</td>
<td>441</td>
<td>479</td>
<td>415</td>
<td>460</td>
<td>465</td>
<td>439</td>
</tr>
<tr>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>440</td>
<td>465</td>
<td>420</td>
<td>421</td>
<td>468</td>
<td>438</td>
</tr>
<tr>
<td>MCH</td>
<td>411</td>
<td>421</td>
<td>407</td>
<td>391</td>
<td>423</td>
<td>413</td>
</tr>
</tbody>
</table>

<sup>c</sup> Longest wavelength bands, values in nm. <sup>d</sup> 1,2-Cl<sub>2</sub>Et = 1,2-dichloroethane, MCH = methylcyclohexane.

Conclusions

We have described a simple route to symmetrically and unsymmetrically substituted 3,5,6-tetraphenylbenzo-[1,2-5,4-1,2]-difurans 1. Reaction conditions are relatively mild and should be suitable for a variety of substituents beyond those investigated. Fluorescence studies indicate that some of these compounds may have potential use as fluorescent probes.

Experimental Section

All reagents and solvents were purchased from Aldrich Chemical Co. and used as received. Melting points are uncorrected. 1H NMR and 13C NMR spectra were acquired at 300.133 and 75.469 MHz, respectively, in deuterated chloroform (CDCl<sub>3</sub>) solution using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ). Fluorescence quantum yields were measured on solutions having an optical density of 0.05. An ethanol solution of anthracene of relative viscosity of 1.18 was used as a reference (ϕ = 0.7%). Elemental analyses were performed by Spang Microanalytical Laboratory in Eagle Harbor, Michigan.

General Friedel–Crafts Procedure. A dichloromethane solution of 1,3-dimethoxynaphthalene (1.0 equiv) and aryl chloride (2.10 equiv) was added dropwise to a stirred suspension of aluminum chloride (2.10 equiv) in dichloromethane under nitrogen. Once addition was complete, the reaction mixture was left to stir at room temperature for 72 h. The resulting solution was then poured over a mixture of crushed ice and conc HCl (3:1). The organic layer was separated and washed with an aqueous 5% KOH solution (6 × 25 ml). The base extracts were combined, neutralized with conc HCl, and extracted with diethyl ether. The ether extracts were dried (MgSO<sub>4</sub>), and solvent was removed under reduced pressure. The resulting residue was triturated with methanol to afford 1,3-dihydroxy-4,6-diarylnaphtalene as a crude solid.

1,3-Dihydroxy-4,6-dibenzoylnaphtalene (9a). Sublimation in vacuo (0.1 Torr, 120–135 °C), followed by recrystallization from MeOH (5%), afforded colorless crystals, mp 147–149 °C. 1H NMR δ 6.63 (s, 1H), 7.25–7.60 (m, 5H), 8.01 (s, 1H), 12.88 (s, 1H); 13C NMR δ 105.37, 112.73, 128.37, 128.8, 132.11, 137.24, 142.63, 169.76, 199.91. Anal. Calcd for C<sub>20</sub>H<sub>14</sub>O: C, 75.66; H, 4.49.

following the disappearance of the OCH₂Ar protons. Once the reaction had gone to completion, the solvent was removed under reduced pressure to afford a mixture of isomers of 4 as yellow powder. In all cases, spectral data and elemental analysis revealed that the crude product mixture required no further purification.

2.6-Dihydroxy-2,5,5,6-tetraphenyl-2,5,5,6-tetrahydrobenzo[1,2-b:5,4-b']difuran (12a): 1H NMR δ 3.77 (s, 3H), 6.56 (s, 1H), 6.7–7.8 (m, 20H); 13C NMR δ 55.59, 93.42, 94.03, 95.08, 101.34, 110.74, 112.59, 114.17, 128.39, 129.71, 130.99, 141.22, 144.97, 156.48, 156.61, 161.66, 160.71, 160.9, 161.04. Anal. Calcd for C₃₃H₂₈O₇N: C, 79.84; H, 4.46; N, 2.34. Found: C, 78.74; H, 4.46; N, 3.42.

2.6-Dihydroxy-2,5,5,6-tetraphenyl-2,5,5,6-tetrahydrobenzo[1,2-b:5,4-b']difuran (12b): 1H NMR δ 3.86 (s, 3H), 6.63–7.8 (m, 20H); 13C NMR δ 55.59, 58.42 (ms), 93.41, 94.33, 95.71, 95.86, 95.9, 96.70, 112.38–123.94, 140.18, 142.20, 150.4, 152.2, 153.98, 160.33, 161.3, 164.64–163.54. Anal. Calcd for C₃₃H₂₈O₇N: C, 78.14; H, 4.48; N, 2.63. Found: C, 78.04; H, 4.75; N, 2.44.

2.6-Dihydroxy-2-(4-cyanophenyl)-6-(3,5-dimethoxyphenyl)-2,5,5,6-tetrahydrobenzo[1,2-b:5,4-b']difuran (12c): 1H NMR δ 3.54–3.8 (ms, 3H), 5.69 (s, 1H), 6.31–7.45 (m, 18H); 13C NMR δ 55.23, 58.92, 93.87, 96.14, 99.40, 100.95, 101.06, 101.2, 104.32, 104.46, 104.55, 107.17, 107.23, 116.23, 118.07, 126.75, 129.5, 132.46, 133.87, 134.56, 138.58, 160.61, 161.66, 160.71, 160.9, 161.04. Anal. Calcd for C₃₃H₂₈O₇N: C, 78.14; H, 4.48; N, 2.63. Found: C, 78.04; H, 4.75; N, 2.44.
137.44, 155.44, 158.70, 160.64, 160.65, 160.94, 161.01. Anal. Caled for CsH8O2: C, 73.81; H, 5.49. Found: C, 74.45; H, 5.81.

2,6-Dihydroxy-2-(4-cyanophenyl)-6-(4-methoxyphenyl)-3,5-bis(4-methylphenyl)-2,3,5,6-tetrahydrobenzol[1,2-b,5,4-b'-]difuran (1b): [H NMR δ 2.41 (s, 3H), 2.44 (s, 3H), 3.80 (s, 3H), 3.80 (s, 1H), 6.50-7.50 (m, 18H); _13C NMR δ 21.05, 21.09, 25.35, 55.28, 93.91, 109.33, 113.55, 117.55, 126.91, 127.59, 127.70, 128.53, 128.98, 129.08, 129.34, 129.08, 129.14, 130.95, 133.06, 150.99, 152.92. Anal. Caled for CsH8O2: C, 88.14; H, 5.34. Found: C, 88.15; H, 5.49.

General Dehydration Procedure. A pyridine solution of 12 (1.0 equiv) and methanesulfonyl chloride (4.0 equiv) was stirred under nitrogen at room temperature for 18 h. The solvent was then removed under reduced pressure, and the crude product was dissolved in dichloromethane and washed three times with a saturated solution of aqueous NaHCO3. The organic layer was separated, dried (MgSO4), and solvent removed under reduced pressure. The residue was triturated with methanol and filtered to afford 1 as crude product. Flash chromatography on silica gel (Aldrich, Merck grade 60, 230-240 mesh, 60 Å) using 2:8 (dichloromethane:hexane) as the eluent followed by solvent removal under reduced pressure. The residue was triturated with methanol and filtered to afford pure 1 as a fluffy powder.

2,3,5,6-Tetraphenylbenzo[1,2-b,5,4-b']difuran (1a): light cream solid (69%), mp 215-216 °C; _1H NMR δ 7.39 (m, 1H), 7.41-7.48 (m, 1H), 7.73 (s, 1H), 7.75 (d, 1H, _J_ = 4); _13C NMR δ 93.91, 109.33, 117.55, 126.91, 127.59, 127.70, 128.23, 128.43, 129.08, 129.94, 130.84, 133.06, 150.99, 152.92. Anal. Caled for CsH8O2: C, 88.25; H, 4.88.

2,6-Bis(4-cyanophenyl)-3,5-diphenylbenzo[1,2-b,5,4-b']difuran (1b): light cream solid (80%), mp 340-341 °C; _1H NMR δ 7.39 (1H), 7.41-7.48 (m, 1H), 7.56 (d, 1H, _J_ = 4), 7.73 (s, 1H), 7.75 (d, 1H, _J_ = 4); _13C NMR δ 93.91, 109.33, 117.55, 126.91, 127.59, 127.70, 128.23, 128.43, 129.08, 129.94, 130.85, 133.06, 150.99, 152.92. Anal. Caled for CsH8O2: C, 84.36; H, 3.93; N, 5.46. Found: C, 84.27; H, 3.99; N, 5.50.

2,6-Bis(4-methoxyphenyl)-3,5-diphenylbenzo[1,2-b,5,4-b']difuran (1c): cream colored solid (63%), mp 212-214 °C; _1H NMR δ 3.82 (s, 3H), 6.85 (d, 1H, _J_ = 4), 7.37-7.50 (m, 5H), 7.58 (d, 1H, _J_ = 4), 7.60 (d, 1H, _J_ = 4); _13C NMR δ 55.21, 69.24, 113.85, 115.85, 123.42, 123.79, 127.70, 128.24, 128.95, 129.84, 133.18, 150.90, 154.40, 155.59. Anal. Caled for CsH8O2: C, 82.72; H, 4.98. Found: C, 83.54; H, 5.01.

2,6-Bis(3,5-dimethylphenyl)-3,5-diphenylbenzo[1,2-b,5,4-b']difuran (1e): pale yellow solid (70%), mp 284-286 °C; _1H NMR δ 3.81 (s, 3H), 6.84 (d, 1H, _J_ = 4), 7.38 (s, 1H), 7.40-7.58 (m, 10H), 7.02 (d, 1H, _J_ = 6), 7.71 (s, 1H); _13C NMR δ 55.28, 93.91, 109.52, 110.68, 113.97, 115.76, 115.80, 128.67, 129.67, 129.82, 128.81, 128.37, 129.08, 129.37, 129.67, 129.82, 132.01, 129.53, 129.84, 127.92, 127.77, 128.88, 130.15, 132.21, 135.08, 137.61, 138.23, 148.26, 150.84, 153.22, 160.66. Anal. Caled for CsH45O4: C, 81.41; H, 5.04; N, 2.24. Found: C, 81.69; H, 5.00; N, 2.30.

Acknowledgment. We would like to thank Prof. Aryeh Frimer of Bar Ilan University for helpful discussions.

JO941110P