

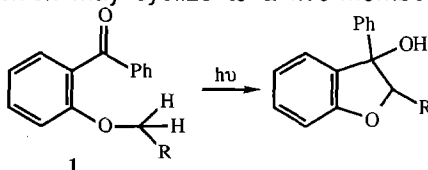
## An Approach to Aflatoxins Using Type II Photocyclization Reactions

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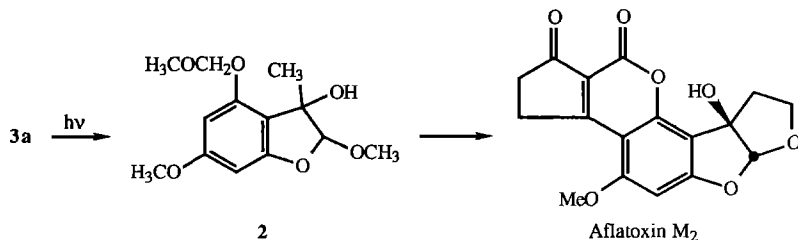
**Summary:** The type II photocyclization of 2,6-disubstituted acetophenones provides a direct synthetic route to a precursor to aflatoxin M<sub>2</sub>.

Hydrogen atom abstraction is a primary photoreaction of ketones and aldehydes.<sup>1</sup> Its synthetic potential has been little studied. One synthetically useful consequence is the type II photocyclization. Normally, this reaction generates a cyclobutanol by a 1,5-hydrogen atom abstraction reaction followed by cyclization of the biradical; however, when the pathway for the formation of a 1,4-biradical is blocked, as in ketone **1**, a 1,5-biradical can be generated which may cyclize to a five-membered ring. This process has

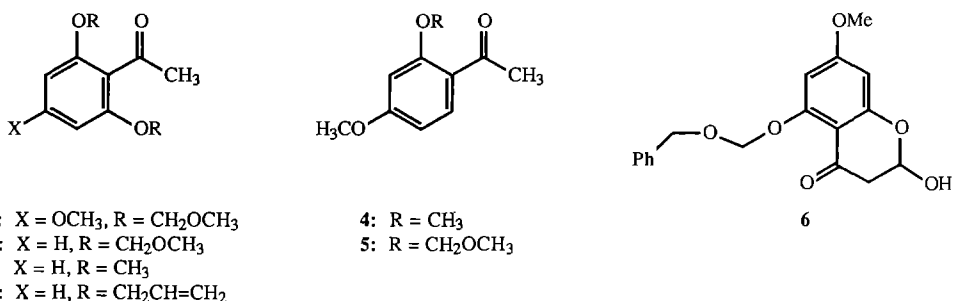


good precedent in ortho-substituted benzophenones<sup>2</sup> and glyoxylates<sup>3</sup>; however, examples with aryl alkyl ketones are rare. Those examples which have been reported are complicated by the intervention of competing reactions such as 2+2 cycloaddition or fragmentation.<sup>4</sup> We report herein several successful examples of five-membered heterocyclic ring formation plus an index for predicting successful cyclizations in this series.

We have been pursuing a direct approach<sup>5</sup> to aflatoxin M<sub>2</sub> which required a convenient preparation of intermediate **2**. Although many of the aflatoxins are readily available, aflatoxin M<sub>2</sub> is scarce. Moreover, there is considerable interest in metabolites of aflatoxin M<sub>2</sub>. Intermediate **2** might be readily prepared from a ketone such as **3a** by a



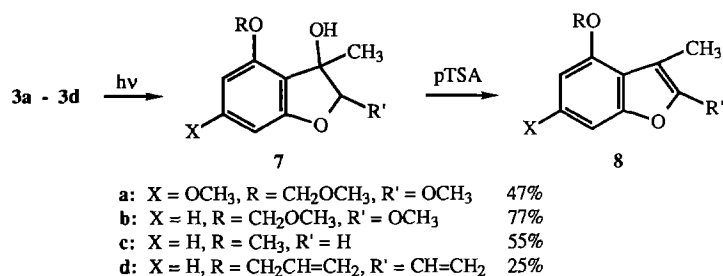
type II photocyclization. Pioneering studies by Wagner and coworkers indicated that electron donating groups dramatically decreased the quantum yields for hydrogen atom abstraction due to low equilibrium levels of the  $n\text{-}\pi^*$  state.<sup>6</sup> However, examination of molecular models revealed that the carbonyl in **3a-3d** would likely exist in a



conformation wherein it was almost orthogonal to the aromatic ring. Therefore, compounds **3a-3d** might react more like aliphatic ketones, with the influence of the alkoxy groups largely attenuated. As support for this hypothesis, the ultraviolet spectrum of **9** exhibited an absorption maxima at 232 nm, compared to 260 nm calculated by the method of Scott.<sup>7</sup> Ketones **4**, **5** and **6** which could adopt a planar conformation were also examined.

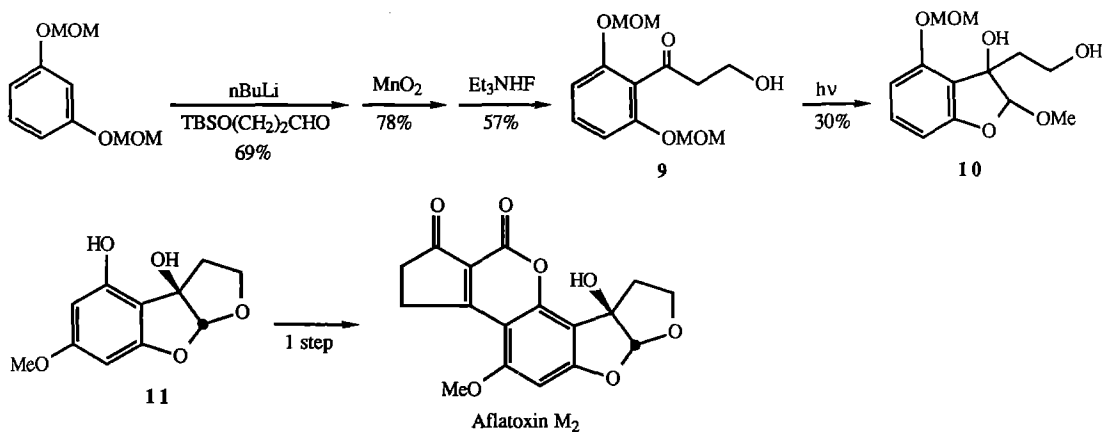
Compounds **3-6** were subjected to photolysis in benzene at ambient temperature under a nitrogen atmosphere using a medium pressure Hanovia lamp. Irradiation times on preparative scales (5-10 mmol) were 6-15 hours. Ketones **3a-3d** afforded the desired dihydrobenzofuranols **7a-7d** in good yields. These products were dehydrated by silica gel chromatography. Treatment of **7a-7d** with a catalytic amount of pTSA in benzene at 25°C also produced the corresponding benzofurans **8a-8d** in excellent yields.<sup>8</sup>

Interestingly, the photocyclization of acetals **3a** and **3b** proceeded much more effectively than the allyl ether **3d**. Perhaps this suggests some electron transfer component in the cyclization. Ketones **4**, **5** and **6** yielded only recovered starting



materials after irradiation for 12 hours. Presumably, these ketones exist in a conformation with the ketone carbonyl in the plane of the aromatic ring. Whatever photochemistry occurs probably originates from the  $\pi$ - $\pi^*$  state, which is not prone to hydrogen atom abstraction.

The keto alcohol **9** was then prepared as shown below.<sup>9</sup> The bis-methoxymethyl derivative of resorcinol was metallated with *n*-BuLi in boiling ether and then reacted with the aldehyde. The resulting carbinol was oxidized with manganese dioxide and deprotected with triethylammonium fluoride to furnish **9**. Irradiation of **9** afforded **10** in 30% isolated yield after silica gel chromatography. The chromatographic stability of **10** may be due to inductive effects or to intramolecular hydrogen bonding.



In view of the conversion of **11** into aflatoxin M<sub>2</sub> in one step by Buchi,<sup>10</sup> the synthesis of dihydrobenzofuranol **10** augurs well for a direct photochemical entry to the aflatoxin family.

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8. Representative spectra: **7c**: NMR (CDCl<sub>3</sub>) 1.78 (s, 3 H), 2.40 (s, 1 H), 3.86 (s, 3 H), 4.27 (d, J = 11 Hz, 1 H), 4.47 (d, J = 11 Hz, 1 H), 6.42-6.54 (m, 2 H), 7.18 (t, J = 8 Hz, 1 H). MS: m/e 91, 107, 147, 165, 180. HRMS: m/e for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub> calcd. 180.07865, found 180.07863. **8c**: NMR (CDCl<sub>3</sub>) 2.34 (s, 3 H), 3.91 (s, 3 H), 6.61 (d, J = 8 Hz, 1 H), 7.04 (d, J = 8 Hz, 1 H), 7.16 (t, J = 8 Hz, 1 H), 7.25 (bs, 1 H).
9. Diol **10** appeared to be one diastereomer. NMR (CDCl<sub>3</sub>) δ 2.03-2.11 (m, 1 H), 2.35-2.43 (m, 1 H), 2.66 (t, J = 5.8 Hz, 1 H, exchangeable by D<sub>2</sub>O), 3.51 (s, 3 H), 3.63 (s, 3 H), 3.78-3.96 (m, 2 H), 5.21 (s, 1 H), 5.22 and 5.27 (ABq, J = 6.6, 2 H), 6.51 (d, J = 8.4, 1 H), 6.71 (d, J = 8.4, 1 H), 7.15 (t, J = 8.4, 1 H). IR (CDCl<sub>3</sub>) 3540, 2940, 1605, 1480, 1250, 1150, 1040 cm<sup>-1</sup>. MS: m/e 121, 147, 163, 177, 190, 208, 220, 252. HRMS: m/e for C<sub>13</sub>H<sub>18</sub>O<sub>6</sub>: calcd. 270.11034, found 270.1095. CMR (CDCl<sub>3</sub>) δ 39.25, 56.25, 56.72, 59.24, 81.35, 94.19, 104.66, 107.79, 108.73, 117.55, 130.99, 154.91, 158.13.
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