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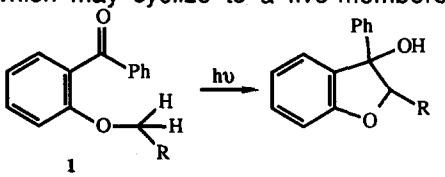
An Approach to Aflatoxins Using Type II Photocyclization Reactions

George A. Kraus*, P.J. Thomas and Mark D. Schwinden
Department of Chemistry, Iowa State University, Ames, Iowa 50011

Summary: The type II photocyclization of 2,6-disubstituted acetophenones provides a direct synthetic route to a precursor to aflatoxin M_2.

Hydrogen atom abstraction is a primary photoreaction of ketones and aldehydes.[1] 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



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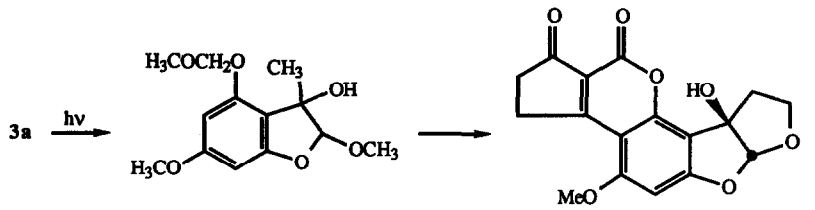
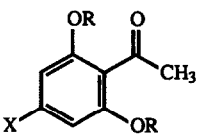
good precedent in ortho-substituted benzophenones[2] and glyoxylates[3]; however, examples with aryl alkyl ketones are rare. Those examples which have been reported are complicated by the intervention of competing reactions such as 2+2 cycloaddition or fragmentation.[4] We report herein several successful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

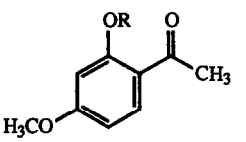
We have been pursuing a direct approach[5] to aflatoxin M_2 which required a convenient preparation of intermediate **2**. Although many of the aflatoxins are readily available, aflatoxin M_2 is scarce. Moreover, there is considerable interest in metabolites of aflatoxin M_2. Intermediate **2** might be readily prepared from a ketone such as **3a** by a

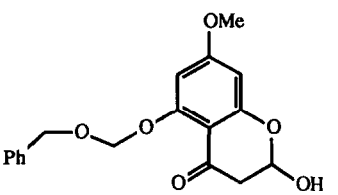


2 Aflatoxin M_2

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-π^* state.[6] However, examination of molecular models revealed that the carbonyl in **3a-3d** would likely exist in a







3a: X = OCH_3, R = CH_2OCH_3
3b: X = H, R = CH_2OCH_3
3c: X = H, R = CH_3
3d: X = H, R = $CH_2CH{=}CH_2$

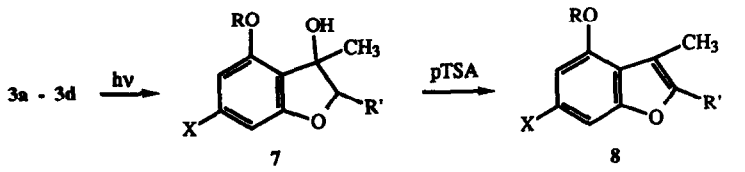
4: R = CH_3
5: R = CH_2OCH_3

6

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 suppport 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.[7] 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.[8]

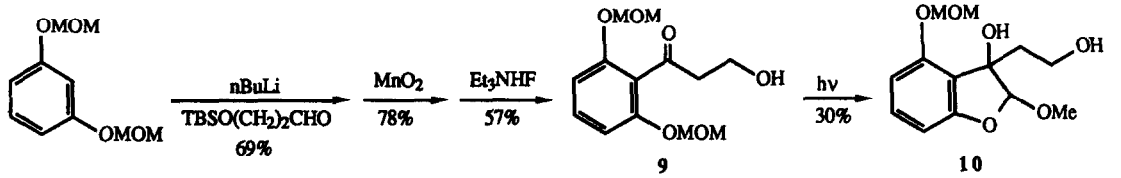
Interestingly, the photocyclization of acetals **3a** and **3b** proceeded much more effectively than the allyl ether **3d**. Perhaps this suggests some electron transfer component in the cyclization. Ketones **4**, **5** and **6** yielded only recovered starting

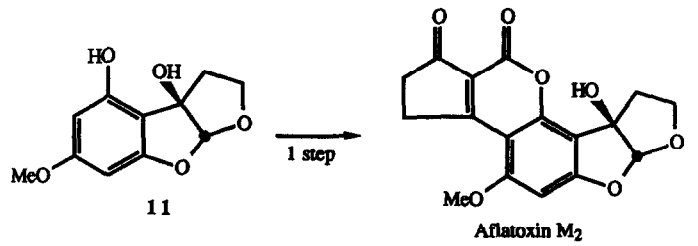


a: X = OCH_3, R = CH_2OCH_3, R' = OCH_3 47%
b: X = H, R = CH_2OCH_3, R' = OCH_3 77%
c: X = H, R = CH_3, R' = H 55%
d: X = H, R = $CH_2CH{=}CH_2$, R' = $CH{=}CH_2$ 25%

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 π-π^* state, which is not prone to hydrogen atom abstraction.

The keto alcohol **9** was then prepared as shown below.[9] 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_2 in one step by Buchi,[10] the synthesis of dihydrobenzofuranol **10** augurs well for a direct photochemical entry to the aflatoxin family.

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7. A.I. Scott *Interpretation of Ultraviolet Spectra of Natural Products* (Pergamon Press, Oxford, 1964).
8. Representative spectra: **7c**: NMR ($CDCl_3$) 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 $C_{10}H_{12}O_3$ calcd. 180.07865, found 180.07863. **8c**: NMR ($CDCl_3$) 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 ($CDCl_3$) δ 2.03-2.11 (m, 1 H), 2.35-2.43 (m, 1 H), 2.66 (t, J = 5.8 Hz, 1 H, exchangable by D_2O), 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 ($CDCl_3$) 3540, 2940, 1605, 1480, 1250, 1150, 1040 cm^{-1}. MS: m/e 121, 147, 163, 177, 190, 208, 220, 252. HRMS: m/e for $C_{13}H_{18}O_6$: calcd. 270.11034, found 270.1095. CMR ($CDCl_3$) 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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