ON THE STEREOSELECTIVITY OF

HETEROATOM DIRECTED PHOTOARYLATION

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Photocyclizations of 4-ally1-3-methy1-2-aryloxy-2-cyclohexen-1-ones occur by steric approach control to give benzodihydrofurans with the 4-ally1 substituent <u>trans</u> to the aryl group.

Photocyclization of 2-aryloxy- and 2-thioaryloxyenones has been demonstrated to occur by <u>conrotatory electrocyclization</u> to give an ylide, from which suprafacial 1,4-hydrogen migration gives a <u>trans</u>-fused dihydrofuran, while ylide-solvent proton transfer gives a <u>cis</u>-fused dihydrofuran.¹ In systems such as $\underline{A} \rightarrow \underline{B} \rightarrow \underline{C}$, two conrotatory cyclizations are possible, but only one has been observed. In these examples, photocyclization appears to be governed by product development control to give the relatively strain free delocalized ylide <u>B</u> with a <u>cis</u>-decalone-like ring fusion; the corresponding ylide with a <u>trans</u>-ring fusion is exceedingly strained.



We wondered if product development control would operate for other systems in which the overriding constraint of ring strain is not present. As part of a program designed to explore the synthetic utility of heteroatom directed photoarylation in the context of morphine alkaloid synthesis, we undertook a study of the stereoselectivity of 4-allyl-3methyl-2-aryloxy-2-cyclohexen-1-one (<u>1</u>) photocyclization.² Pyrex-filtered irradiation of <u>la</u> (oil) in benzene-methanol solution (1:1, 0.06M) for 2.5h gives a mixture of dihydrobenzofurans $\underline{2a}$ (major isomer shown), diastereoisomeric at C(4) in 88% chromatographically isolated yield. Attempted VPC analysis of $\underline{2a}$ results in decomposition. However, catalytic hydrogenation of $\underline{2a}$ gives $\underline{3a}$ (96% yield) and VPC analysis of $\underline{3a}$ reveals the presence of a two component mixture in a ratio of 8.4:1.0. While we have not been able to separate these diastereoisomers, we believe that the dominant product of the photocyclization of $\underline{1a}$ (~ 90%) is that presented in formula $\underline{2a}$. This supposition is based on the following stereorational conversion of $\underline{2a}$ to $\underline{9}$ and $\underline{10}$ (13:1).



Reduction of the reaction mixture from irradiation of la with excess Al(Hg) in THF: H_{20} (10:1, 0.1 M) for 90 min at room temperature gives hemiketal 4 (95% yield). Reaction of 4 with lithium tetramethylpiperidide (2 equiv) in THF-HMPA solution at -78°C followed by addition of tert-butyldimethylsilyl chloride and warming to room temperature gives a phenolic silyl ether enol silyl ether; ketalization (methanol, trimethylorthoformate, p-toluenesulfonic acid) followed by filtration chromatography on alumina gives 5a in 80% yield. Ozonolysis in CH_2Cl_2 followed by reduction with zinc and acetic acid gives aldehyde 5b (oil, 95%), which, on treatment with Jones reagent, gives keto acid 6a (oil, 86%). Conversion of 6a to methyl ester <u>6b</u> with diazomethane in ether is followed by ketalization to give <u>7a</u>. Removal of the phenolic oxygen atom is accomplished by 1) cleavage of the silyl ether in 7a with tetra-nbutylammonium fluoride in THF to give 7b (61%); 2) reaction of 7b with excess K_2CO_3 and 5-chloro-l-phenyl-lH-tetrazole (2 equiv) in DMF at room temperature to give 7c (70%); 3) hydrogenolysis of tetrazole 7c (Pd/C in EtOAc); filtration of the partially deketalized product through neutral alumina gives keto ester <u>8a</u> in 86% yield. The keto group in 8a is reductively removed by conversion to thioketal 8b (3 equiv propane-1,3-dithiol and 0.3 equiv BF_3 ·Et₂0 in methylene chloride solution) and desulfurization of 8b (excess

Raney nickel in refluxing EtOH:THF solution) to give <u>8c</u> in 83% overall yield; saponification of <u>8c</u> (KOH in methanol) gives carboxylic acid <u>8d</u> (88%). Cyclodehydration of <u>8d</u> with polyphosphoric acid at 80°C for 2 h and subsequent silica gel chromatography gives a mixture of two tricyclic ketones in 76% isolated yield. The major product (93%) is the <u>trans</u>-fused 9-keto octahydrophenanthrene <u>9</u>, while the minor product is the corresponding <u>cis</u>-isomer <u>10</u> (7%), as determined by comparison (VPC and 'H NMR analysis) to authentic <u>9</u> and <u>10</u>.³



In a discussion of the factors governing the stereoselectivity of heteroatom directed photoarylation, we must consider the character of the transition state⁴ involved in the electrocyclization process. An early transition state for electrocyclization, which resembles the geometry of the starting aryloxyenone, would be expected to be subject to steric approach control. If we assume that <u>D</u> is a representation of the excited state of <u>la</u>, then, for an early transition state, the phenyl group should approach C(3) from the least sterically hindered face of the C(2)-C(3) double bond, <u>trans</u> to the allyl group.⁵ This transition state picture for ylide formation leads to the conclusion that the predominant dihydrofuran resulting from ylide rearrangement ought to be that, as observed for <u>la</u>, with the allyl group <u>trans</u> to the phenyl group.

On the other hand, a late transition state for electrocyclization should resemble the ylide, here represented by the carbonyl delocalized formula E. Clearly, there is the poten-

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tial for serious steric crowding between the allyl substituent and a group R_2 on the aromatic ring. Derivatives <u>lb</u> and <u>lc</u> provide a test for the importance of late transition state geometry.



Pyrex-filtered irradiation of <u>1b</u> (mp 116-117°C) in benzene-methanol solution gives a clean reaction mixture, from which cyclized product <u>2b</u> can be obtained in 86% chromatographically isolated yield. Proton NMR data indicate that diastereomeric purity is greater than that already recorded for <u>1a</u>; hydrogenation of the photoproduct mixture gives crystalline <u>3b</u> (mp 104-105°C, 75%), which appears to be a single component by VPC analysis. A similar set of experiments was performed with aryloxyenone <u>1c</u> (mp 88-89°C) and <u>1d</u> (mp 73-74°C) with resulting stereoselectivity similar to that observed for 1b.

Thus, the predominant diastereoisomer (> 90%) formed on photocyclization of the series <u>la-ld</u> is that with the 4-allyl substituent <u>trans</u> to the aryl group. These results suggest that photocyclization occurs by steric approach control with an early transition state similar in geometry to formula <u>D</u>.

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References

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- 5. It should be appreciated that a pseudoaxial C(4) allyl group would make an even more convincing argument for approach of the aryl group to the C(2)-C(3) double bond, <u>trans</u> to the allyl group.
- 6. Structural assignments for <u>2b-2d</u> are based on 'H NMR spectral analysis and chemical correlation; <u>e.g.</u>, conversion of <u>2c</u> and <u>2d</u> to <u>3e</u> ($R_1 = 0$ Me, $R_2 = H$; diastereoisomer ratio ~ 13:1.0 from <u>2c</u> and 8.2:1.0 from <u>2d</u>) and conversion of 2d to <u>3a</u>.

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