Pergamon

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Intermolecularly Selective [4+4] Photocycloaddition of 2-Pyridone Mixtures

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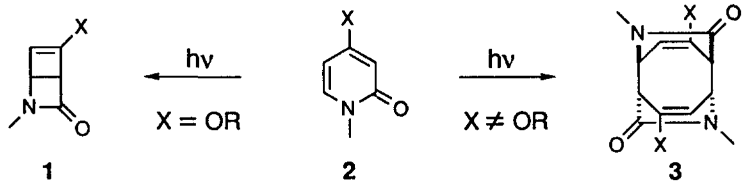
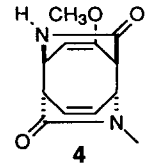
Abstract: 4-Alkoxy-2-pyridones do not undergo [4+4] photodimerization but will react with other 2-pyridones to yield highly functionalized cyclooctadienes with differentiated functional groups.

Photodimerization of 2-pyridones (**2**) to give cyclooctadiene products (**3**) is a well studied [4+4] cycloaddition that is general for a variety of substituted 2-pyridones.[1] Proceeding through a short lived singlet excited state, this dimerization is concentration dependent: above 0.1 M the [4+4] cycloaddition is often the exclusive product, whereas below this photoisomerization to Dewar pyridone **1** dominates.[2] Based on the results of De Selms and Schleigh with the natural product ricinine,[3] Kaneko has shown that 2-pyridones bearing a 4-alkoxy substituent react anomalously, resisting dimerization and giving only the Dewar pyridones **1**.[4] The origins of this altered reactivity are not known.



As a part of an ongoing investigation of intramolecular [4+4] cycloadditions, we needed to know if it was possible for 4-alkoxy-2-pyridones to undergo [4+4] cycloaddition with a 2-pyridone *lacking* the alkoxy substituent. Irradiation of a mixture of 4-methoxy-2-pyridone and *N*-methyl-2-pyridone led to the isolation of a product that was tentatively identified as **4**,[5] and subsequent pursuit of an intramolecular variation.[6] Although **4** was produced in low yield, we were intrigued by the high degree of differentiated functionality and its origin from very simple starting material. Pyridones have been found to undergo [4+4] photocycloaddition with cyclopentadiene[7] and with 2-methyl-[1,2,4]triazolo[1,5-*a*]pyridines,[8] but photochemistry with 2-pyridone mixtures has not received attention. We report here our initial results from further investigation of this intermolecular reaction and the significant effects of stoichiometry on the outcome.



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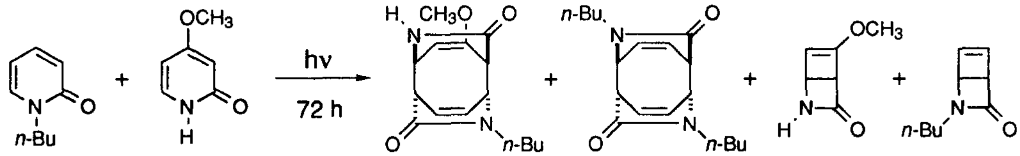
For this work we chose to study the reaction of *N*-butyl-2-pyridone **5** with 4-methoxy-2-pyridone **6**, anticipating that the use of lipophilic **5** and acidic **6** would make separation of the anticipated product mixture straightforward. In the event, pyrex-filtered irradiation of a 1:1 mixture of these 2-pyridones for 72 h (0.25 M for each in methanol, see Table) led to recovery of nearly half of the starting **5**. Two trans [4+4] products were isolated, cross product **7** and the dimer **8**, in yields of 6% and 22%, respectively (11% and 40%, based on unrecovered **5**).[9] Surprisingly however, the simultaneous *formation of photoproduct* **9** *was* not *observed and 97% of the unreacted* **6** *was recovered unchanged.*[10,11]

We suspected that formation of the cross product **7** might be favored by simply increasing the concentration of unreactive pyridone **6** relative to pyridone **5**. That increasing the concentration of **6** could be accommodated in this photoreaction was anticipated from the absorption characteristics of the two reactants; pyridone **5** has a typical 2-pyridone absorption with a λ_{max} of 302 nm ($\varepsilon = 5{,}600$) while the presence of the methoxy group in **6** shifts the absorption to shorter wavelengths ($\lambda_{max} = 278$ nm) and attenuates the extinction coefficient ($\varepsilon = 3{,}750$). With a pyrex filter blocking wavelengths below 290 nm, we assume that the observed photochemistry is initiated by excitation of **5**, followed by reaction with ground state molecules **5** or **6**.

This speculation proved fruitful and changing the ratio of starting pyridones from 1:1 to 1:4 dramatically changed the outcome. After 72 h all of the initial pyridone **5** was consumed and the cross product **7** exceeded the dimer **8** by more than a factor of 7! Only a trace of Dewar pyridone **10** was found, Dewar pyridone **9** was not observed, and 90% of the unreacted **6** was recovered unchanged.[11]

In addition to the products shown in the Table, the less stable cis isomers **11** and **12** were also isolated and characterized.[12] The yield for these photocycloaddition products were substantially less than the trans isomers **7** and **8** and the isolated yields were quite variable, often including **13**, **14**, and **15** derived from the Cope rearrangement of **11** and **12**. Based on our experience with the intramolecular [4+4] photoproducts of 2-pyridones,[13] we expect that thermal rearrangement of **11** and **12**, coupled with the photocleavage of **13**–**15**, will lead to higher yields of the trans isomers **7** and **8**.

Table. Product ratio from irradiation of a mixture of **5** and **6** is highly dependent on initial concentrations.



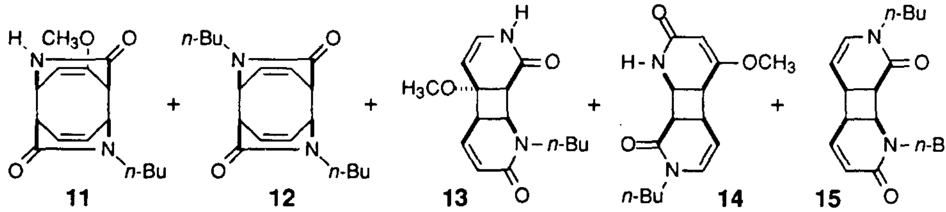
5 **6** **7** **8** **9** **10**

(cnvrsn 5)	ratio	(rcvrd 6[a])		molar ratio		Isolated yields[b]	
(55%)	1 : 1	(97%)	6%	1 : 1.8	22%	0%	2%
(100%)	1 : 4	(90%)	42%	7.2 : 1	12%	0%	1%

[a] see reference 11. [b] Isolated yields based on initial quantity of 5.

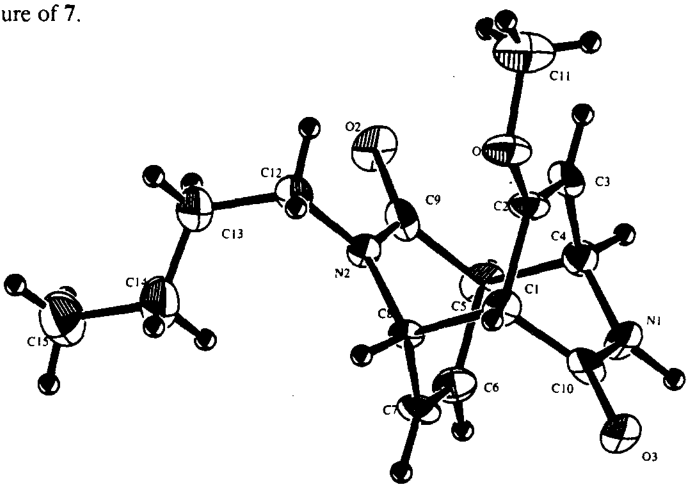
The data presented in the Table does not allow for a determination of the intrinsic reactivity of the two chromophores **5** and **6**. In addition to the formation of minor isomers such as **10** and the potential complication from reactivity of the cis isomers,[13] the relative ratio of reactants **5** and **6** change during the course of the reaction. In the formation of both **7** and **8**, pyridone **5** is consumed faster than **6**, and as the reaction proceeds the ratio of **5**:**6** becomes larger. In the case where **5** is fully consumed, the greatly enhanced production of **7** and diminished yield of **8** is easily understood.

Figure 1. Minor products and secondary reaction products formed during the photocycloaddition of **5** and **6**.



The structure of the major product **7** was confirmed, by single crystal X-ray analysis (Figure 2),[14] as having the trans, head-to-tail stereo- and regiochemistry typically found in 2-pyridone photodimers.

Figure 2. X-ray structure of **7**.



The simple technique outlined here allows for the synthesis of [4+4] cycloadducts with differentiated functionality, beginning with very simple starting materials. The significant differences between secondary and tertiary amides,[15] and the differences in alkene and enol ether reactivity should allow for the systematic elaboration of **7**. Further enhancement of the ratio of products might be achieved through small alterations in reaction conditions, such as slow or incremental addition of **5** to the reaction vessel.

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9 The yields for **9** and **10** are based on **5** as the limiting reagent. The ratio of the products is calculated as the relative molar quantities of cycloadducts products.

10 The apparent difference in the experimental details of our procedures and those of Kaneko are the use of a medium pressure mercury lamp (ours) versus a high pressure mercury lamp.

11 The calculated quantity of recovered pyridone **6** takes into account the quantity consumed in the formation of **11** as well as **13** and **14**, typically 15-20% overall yields based on the amount of **5** consumed in the reaction.

12 All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, MS and combustion analysis.

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14 Compound **7** crystallizes from dichloromethane in the monoclinic space group $P2_1/n$ with $a = 14.088$ (4) Å, $b = 6.5717$ (9) Å, $c = 15.118$ (4) Å, $\beta = 94.78$ (1)°, $V = 1394.8$ (6) Å^3, and $Z = 4$. Final least squares refinement using 934 unique reflections with $I > 3\sigma(I)$ gave $R(R_w) = 0.067$ (0.071).

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