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Asymmetry by Electrophilic Rearrangement of Symmetric 2-Pyridone Photodimers

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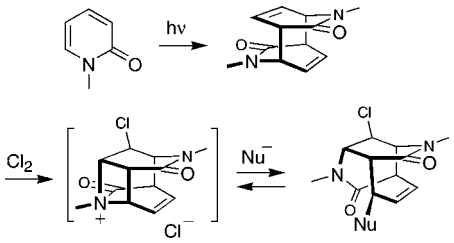
ABSTRACT



Halogenation of achiral *trans*-2-pyridone photodimers results in 1,3-migration of an amide nitrogen and formation of a chiral structure with six stereogenic centers and well-differentiated functionality. The reactivity of this product toward nucleophiles, including the allylic halide, is dominated by participation by the amide nitrogen.

Photodimerization of 2-pyridones is an efficient and regioselective higher order cycloaddition that transforms two achiral aromatics into a cyclooctadiene with four stereogenic centers and functionality at every carbon.[1] This dimerization has been known for four decades but, despite the terpenoid carbon skeleton of the products (**2** and **3**, Scheme 1), has seen few applications.[2] This is due in part to the symmetry of the photoproducts and the recognition that most synthetic targets are not symmetric, requiring some method for selectively manipulating identical substituents of the photodimer.[3]

One solution to the symmetry issue is to react two different pyridones, either intramolecularly[4] or using a method for achieving intermolecular selectivity between two different pyridones.[5] Both solutions add a level of complexity. We describe here that halogenation of the dimer is a simple method that leads to a functionally differentiated product.

As part of our study of 2-pyridone photodimer chemistry directed at accessing polyquinane structures, we described the chlorination of *cis* photodimer **2** (Scheme 1). Only one face of each alkene is accessible to electrophiles and opening of a chloronium ion leads to trapping by the nearby alkene, creating a diquinane carbon skeleton. The resulting carbo-

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(1) Sieburth, S. McN. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; pp 103/1−103/18.

(2) Sieburth, S. McN. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI: Greenwich, CT, 1999; Vol. 5, pp 85−118.

(3) For asymmetric reduction of a centrosymmtric *trans*-2-pyridone photodimer ,see: Spivey, A. C.; Andrews, B. I.; Brown, A. D.; Frampton, C. S. *J. Chem. Soc., Chem. Commun.* **1999**, 2523−2524. See also: Holland, J. M.; Lewis, M.; Nelson, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4082−4084. Anstiss, M.; Holland, J. M.; Nelson, A.; Titchmarsh, J. R. *Synlett* **2003**, 1213−1220.

(4) Sieburth, S. McN.; Chen, J.-l. *J. Am. Chem. Soc.* **1991**, *113*, 8163−8164.

(5) Sieburth, S. McN.; Lin, C.-H.; Rucando, D. *J. Org. Chem.* **1999**, *64*, 950−953. See also: Sato, E.; Ikeda, Y.; Kanaoka, Y. *Liebigs Ann. Chem.* **1989**, 781−788.

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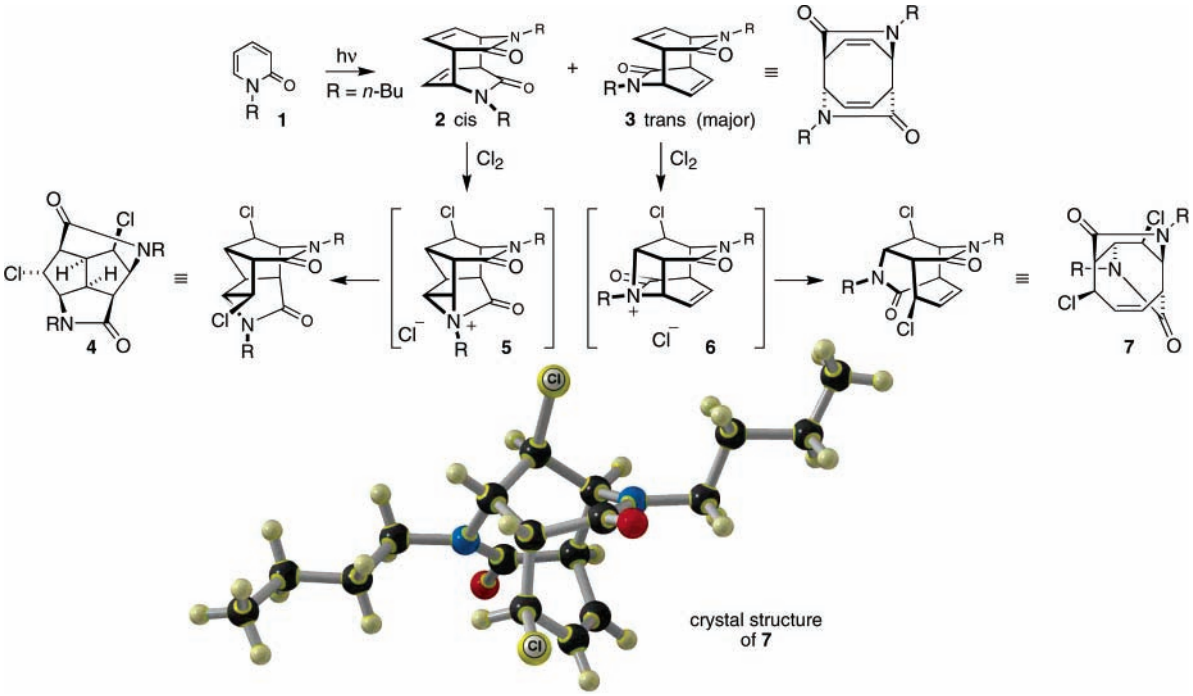
Scheme 1. Amide Nitrogen Migration Occurs in Both Trans and Cis Isomers during Chlorination of the Photoproducts



cation is then intercepted by the adjacent amide nitrogen, forming aziridinium intermediate **5**. Opening of the aziridinium with chloride then yields the observed product **4**.[6]

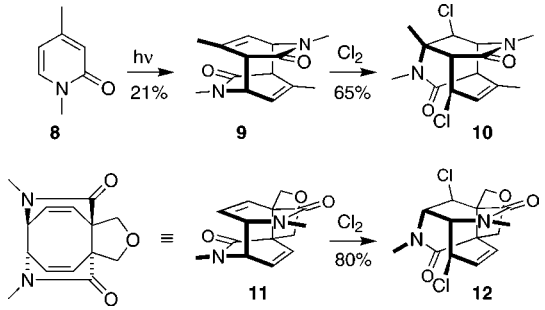
The *trans* isomer **3**, more readily prepared and isolated than **2**, also has alkenes with a single accessible face but the two alkenes cannot interact, so reactions with electrophiles must take a different path.

Addition of chlorine to a solution of the known *trans* dimer **3**[7] leads to a single new product incorporating 1 equiv of chlorine and retaining one alkene, isolated in >90% yield. The structure of this product was confirmed as **7** by X-ray crystallography. In this molecule, the eight-membered carbon ring remains intact, while one of the amide nitrogens has undergone a 1,3-migration. The original point of attachment for the amide nitrogen has a chlorine substituent with stereochemistry indicating that the nitrogen was displaced via an S_N2 process, suggestive of a von Braun reaction, although we are unaware of any example of a von Braun reaction initiated by addition of halogen to an unsaturated amide.[8] Most intriguingly, this high-yielding transformation of **3** into **7** yields a product with well-differentiated functionality. Substitution of bromine for chlorine yields an analogous dibromide, but iodine does not react with **3**.

Migration of the amide nitrogen during this reaction is similar to the participation of the amide nitrogen in the conversion of **2** to **4**, Scheme 1. In the mechanism proposed for the formation of **4**, a three-membered aziridinium intermediate **5** was cleaved by chloride, whereas the mechanism leading to **7** likely involves a four-membered azetidinium ion **6**.

Two additional examples illustrate the generality of the chlorination chemistry for the [4 + 4] pyridone photoadducts, Scheme 2. Head-to-tail dimer **9** is derived from 1,4-dimethyl-

Scheme 2. Additonal Examples of 2-Pyridone Chlorination



2-pyridone **8**. Addition of chlorine to **9** yields **10** in which the nitrogen has migrated to a *tert*-alkyl position. Head-to-head [4 + 4] adduct **11** rearranges to the corresponding allylic chloride **12**. The rearrangements in both examples proceed with good-to-excellent isolated yields, and the product structures **10** and **12** have been determined by X-ray crystallography.

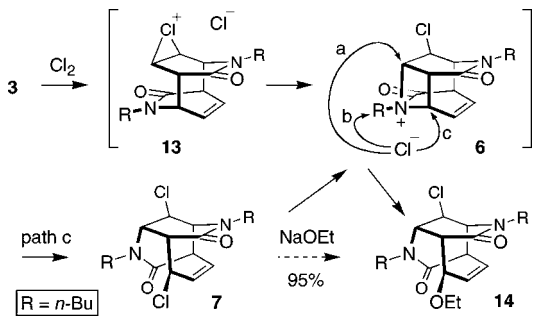
During chlorination of **3**, interception of the initially formed chloronium ion **13** by the proximal amide nitrogen leads to **6**, Scheme 3. The chloride nucleophile has three possible carbon−nitrogen bonds in **6** that could react.

(6) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. McN. *Org. Lett.* **2001**, *3*, 2165−2167.

(7) Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187−1191.

(8) Reviews: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1−7. Hageman, H. A. *Org. React. (N.Y.)* **1953**, *7*, 198−262.

Scheme 3. Potential Pathways for Halogenation and Reactivity of the Product with Sodium Ethoxide

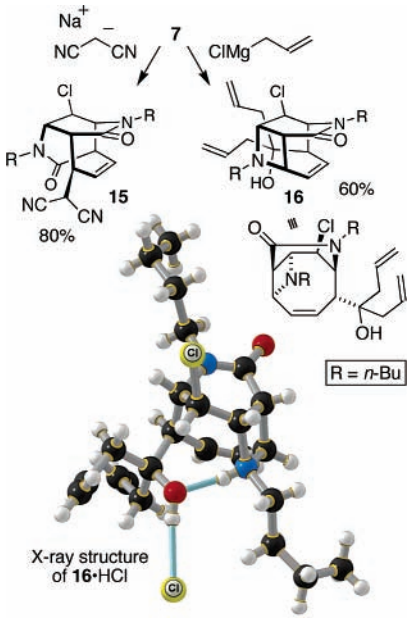


Cleavage of the R group by path b, especially for the *N*-methyl substrates **9** and **11**, would have the least steric hindrance but would yield a highly strained amide product. Path a would yield a *cis* chlorination product and would seem most likely based on amide orbital overlap considerations, but this product is not observed. The allylic nature of the bond that is broken to give **7**, path c, apparently contributes to the observed reactivity by stabilizing the incipient S_N2 transition state.

The dominance of the amide nitrogen in the reactivity of this system can be seen in the treatment of **7** with nucleophiles. The allylic chloride in **7** is notable for the orthogonality of the carbon−chlorine bond to the π-bond of the alkene (see crystal structure, Scheme 1). Without conformational change, S_N2' reactivity would therefore be unexpected, and **7** is a fairly inflexible structure. Moreover, direct S_N2 reaction with an external nucleophile would be parried by the amide that lies in the S_N2 pathway. Warming **7** with sodium ethoxide leads to clean and high yield displacement of one of the chlorides, to give **14** with retention of stereochemistry. Apparently, the most accessible reaction pathway is the reversion of dichloride **7** to the azetidinium ion, followed by nucleophilic attack by the ethoxide, leading to the double inversion and the observed stereochemistry. The stereochemistry of **14** was initially identified by NMR and then confirmed through a crystal structure.

To probe carbon−carbon bond formation, **7** was treated with both sodium malononitrile and allyl magnesium chloride, revealing an additional reaction pathway, Scheme 4. The soft malononitrile anion participates in the double-inversion pathway, introducing the carbon at the allylic position, structure **15**. In contrast, the harder Grignard reagent adds to the azetidinium carbonyl group, consuming two equivalents of reagent and forming a tertiary alcohol **16**. The alcohol of **16** is intramolecularly hydrogen bonded to the azetidine, which can be clearly seen in the proton NMR

Scheme 4. Reactivity of **7** with Carbon Nucleophiles



spectrum. A crystal structure of **16** as the hydrochloride salt found the acid protonating the intramolecularly hydrogen bonded alcohol, Scheme 4.

Isolation of azetidine **16** is consistent with the proposed mechanism, Scheme 3, in which the nitrogen mediates the reactions of **7** with nucleophiles. The rather unique arrangement of functional groups in the 2-pyridone [4 + 4] photoadducts endows them with unusual reactivity.

Using two very simple steps, photodimerization and addition of halogen, one can convert achiral aromatic 2-pyridones into complex and highly functionalized polycyclic molecules. Enantioselective addition of an electrophile to the prochiral alkenes of the photodimers **3** or **9** would lead to optically active products.[9] We are continuing to study the reactivity and applications of these readily available structures.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052071E

(9) Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324−2327.