## Tether-enforced reversal of regioselectivity: head-to-head [4 + 4] photocycloaddition of 2-pyridones

## Scott McN. Sieburth\*† and Brian Siegel

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400, USA

Symmetric 3,3'-attachment of a three-atom chain between two pyridones overrides the head-to-tail regioselectivity found in intermolecular photodimerization reactions and gives a nearly quantitative yield of the head-to-head [4 + 4] cycloadduct containing contiguous quaternary centres.

Photodimerization of 2-pyridones is an efficient [4 + 4] cycloaddition reaction characterized by high regioselectivity and modest stereoselectivity.<sup>1,2</sup> Despite more than thirty five years of study,<sup>3</sup> only one example of a head-to-head product has been described. In that report, Nakamura found that head-to-head regioisomers **3** comprised 11% of the product mixture when the photoreactions were performed in water (Scheme 1).<sup>1</sup> In other solvents, such as ethanol and benzene, only the head-to-tail products **2** were isolated.<sup>4</sup>

In our studies of intramolecular [4 + 4] photocycloadditions<sup>2</sup> between 2-pyridones, the tether has been positioned to reinforce the natural head-to-tail regioselectivity (4, Fig. 1), and these molecules undergo cycloaddition in good to excellent yield.<sup>2d</sup> We report here the first example of symmetrically-tethered 2-pyridones 5, where intramolecular photocycloaddition can only occur with the unnatural head-to-head regiochemistry.<sup>5</sup>

Preparation of photosubstrate 5 utilized the commercially available 2-hydroxynicotinic acid 6 (Scheme 2). This highly insoluble substrate was suspended in toluene and treated with 2 equiv. of hexamethyldisilazane (HMDS) and a catalytic amount of chlorotrimethylsilane.<sup>6</sup> Heating this mixture gave a homogeneous solution containing the bis(trimethylsilyl) derivative 7. This crude product was reduced with diisobutylaluminum hydride to give 3-hydroxymethyl-2-pyridone 8, which was subsequently *N*-methylated to give 9. Recrystallization of 9 gave long (up to 10 cm) needles in 44% overall yield from 6. Treatment of alcohol 9 with thionyl chloride gave the chromatographically unstable chloromethyl derivative 10 which was coupled immediately with another equivalent of



Scheme 1 Nakamura (ref. 1) found head-to-head cycloadducts could be formed as a minor product, but only in aqueous solution



Fig. 1 Tether position enforces regioselectivity

alcohol 9 under phase-transfer conditions<sup>7</sup> to produce photosubstrate 5 in 85% yield.<sup>‡</sup>

Irradiation of 5 was expected to result in a competition between two photochemical options: [4 + 4] cycloaddition and isomerization to Dewar pyridones (11 and 12 versus 13, Scheme 3). Both of these pathways are observed in intermolecular cases, with dilute solutions favouring the unimolecular Dewar product.<sup>1,8,9</sup> Intramolecular reactions do not suffer from concentration effects per se, but the consequence of reversing the natural regioselectivity on the competition between these pathways was unknown. Photoreaction of 5§ proved to be marginally slower than head-to-tail reaction of 4, and after 12 h bis(2-pyridone) 5 was fully converted to two isomeric products in a ratio of 1:1 (98% isolated yield). The [4 + 4] photocycloadditions of 2-pyridones are normally trans selective and therefore we considered the possibility that the alternative photoproduct 13 had formed. Photoisomerization of 5 to Dewar pyridones 13 would be expected to yield a 1:1 mixture through two independent photoisomerization events. Proton NMR spectra of 11 and 12 would also be very similar to that of 13.1 Nevertheless, the IR spectra<sup>‡</sup> of 11 and 12 ruled out the presence of β-lactams and confirmed that cycloaddition remained the exclusive path.

Additional supporting evidence for structures 11 and 12, as well as identification of the *cis* isomer, was derived from heating a methanol solution of the mixture to reflux for 3 h



Scheme 2 Synthesis of photosubstrate 5. *Reagents*: i, HMDS; ii, DIBAL; iii, MeI, K<sub>2</sub>CO<sub>3</sub>, MeOH; iv, SOCl<sub>2</sub>; 9, BnNEt<sub>3</sub>+Cl<sup>-</sup>, 40% NaOH.



Scheme 3 Photocycloaddition of 5 gives exclusively [4 + 4] products

Chem. Commun., 1996 2249



Scheme 4 The *cis* [4 + 4] isomer 12 and its Cope rearrangement product 14 also shown with Chem3D structures

(Scheme 4). Under these conditions the *cis* isomer underwent a quantitative Cope rearrangement to give **14**, while the *trans* isomer **11** remained unchanged (97% combined isolated yield). This facile rearrangement of *cis* [4 + 4] products is also observed for the head-to-tail *cis* products¶-1 and related molecules.<sup>14</sup>

This intramolecular head-to-head photocycloaddition provides ready access to a novel carbocyclic framework from simple aromatic precursors. Studies of this and related systems are continuing.

This research was supported by the National Institutes of Health (GM45214). We thank Fareed N. Fareed for technical support and his participation as part of the NSF REU Program (CHE 9300393).

## Footnotes

† ssieburth@ccmail.sunysb.edu

‡ All new compounds were fully characterized. Selected data for 9: mp 83 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.29 (d, J 7 Hz, 1 H), 7.17 (d, J 7 Hz, 1 H), 6.12 (t, J 7 Hz, 1 H), 4.55 (s, 2 H), 3.55 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) & 162.7, 136.9, 135.8, 131.6, 106.1, 62.1, 37.4; IR (neat) 1648 cm<sup>-1</sup>. For 5: mp 152-153 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.56 (d, J 7 Hz, 2 H), 7.24 (d, J 7 Hz, 2 H), 6.21 (t, J 7 Hz, 2 H), 4.58 (s, 4 H), 3.55 (s, 6 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.8, 136.7, 135.9, 129.6, 105.9, 68.1, 37.6; IR (KBr) 1654 cm<sup>-1</sup>. For 11: mp 164–165 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.42 (m, 2 H), 6.13 (d, J 8.3 Hz, 2 H), 4.61 (d, J 9.0 Hz, 2 H), 3.66 (d, J 9.0 Hz, 2 H), 2.91 (s, 6 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  172.3, 137.5, 131.4, 74.4, 64.0, 61.3, 35.9; IR (KBr) 1651 cm<sup>-1</sup>. For **12**: mp 134–135 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.56 (m, 2 H), 5.76 (d, *J* 8.1 Hz, 2 H), 4.71 (d, J 9.3 Hz, 2 H), 3.58 (d, J 9.3 Hz, 2 H), 2.97 (s, 6 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) & 172.7, 136.2, 134.9, 74.4, 66.5, 62.3, 35.8; IR (KBr) 1662 cm<sup>-1</sup>. For 14: mp 157–159 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.98 (d, J 8.1 Hz, 2 H), 4.74 (d, J 9.1 Hz, 2 H), 4.33 (d, J 9.1, 2 H), 3.95 (d, J 9.1 Hz, 2 H), 3.24 (s, 2 H), 2.99 (s, 6 H);  $^{13}C$  NMR (CDCl<sub>3</sub>)  $\delta$  164.9, 130.6, 102.4, 76.7, 59.7, 41.3, 34.9; IR (KBr) 1657 cm<sup>-1</sup>.

§ A solution of **5** in methanol (0.05 M) in a Pyrex test tube was deoxygenated with a stream of nitrogen for 15 min and then irradiated with a 450 W medium pressure mercury lamp fitted with a Pyrex filter. Removal of the solvent gave a 1:1 mixture of **11** and **12** as the sole products (NMR). These were separated by flash chromatography using 1:9 methanol–dichloromethane.

¶ Products of aromatic [4 + 4] photodimerization, and related molecules such as **11** and **12**, contain new carbon–carbon bonds that are unusually long (*ca*. 1.6 Å) (ref. 10), a feature usually attributed to strain from non-bonding interactions. In contrast to the well known and facile Cope rearrangements of *cis*-1,2-divinylcyclobutanes to cycloocta-1,5-dienes (ref. 11), the thermodynamics are reversed for these types of systems. MM3\* (ref. 12) calculations illustrate this with energies for **11**, **12** and **14** calculated to be 312, 316 and 247 kJ mol<sup>-1</sup> (74.7, 75.5 and 58.9 kcal mol<sup>-1</sup>), respectively. See refs. 13 and 14.

## References

- 1 Y. Nakamura, T. Kato and Y. Morita, J. Chem. Soc., Perkin Trans. 1, 1982, 1187.
- 2 (a) S. McN. Sieburth and J.-I. Chen, J. Am. Chem. Soc., 1991, 113, 8163;
  (b) S. McN. Sieburth and P. V. Joshi, J. Org. Chem., 1993, 58, 1661; (c)
  S. McN. Sieburth and K. Ravindran, Tetrahedron Lett., 1994, 35, 3861;
  (d) S. McN. Sieburth, G. Hiel, C.-H. Lin and D. P. Kuan, J. Org. Chem., 1994, 59, 80.
- 3 E. C. Taylor and W. W. Paudler, Tetrahedron Lett., 1960, 25, 1.
- 4 Head-to-head isomers have also been reported in photoreactions of 2-pyridones in micelles: Y. Nakamura, T. Kato and Y. Morita, *Tetrahedron Lett.*, 1981, **22**, 1025. See also ref. 5.
- 5 Symmetric N,N'-tethered bis(2-pyridone)s have been reported to undergo photocycloaddition but these differ from other cases discussed as the reactions were run with photosensitizers: Y. Nakamura, J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1976, **59**, 2841.
- 6 H. D. H. Showalter and T. H. Haskell, J. Heterocycl. Chem., 1981, 18, 367.
- 7 M. J. Palmer, J. C. Danilewicz and H. Vuong, Synlett, 1994, 171.
- 8 E. J. Corey and J. Streith, J. Am. Chem. Soc., 1964, 86, 950.
- 9 W. J. Begley, G. Lowe, A. K. Cheetham and J. M. Newsam, J. Chem. Soc., Perkin Trans. 1, 1981, 2620.
- 10 X-ray structures of 2-pyridone photoproducts: M. Laing, Proc. Chem. Soc., London, 1964, 343; J. N. Brown, R. L. R. Towns and L. M. Trefonas, J. Am. Chem. Soc., 1971, 93, 7012; S. McN. Sieburth and C.-H. Lin, Tetrahedron Lett., 1996, 37, 1141 and refs. 2(a-c).
- 11 E. Vogel, Liebigs Ann. Chem., 1958, 615, 1.
- 12 Using the MM3 forcefield (ref. 15), as implemented in MACRO-MODEL, ver. 4.0; F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, J. Comp. Chem., 1990, 11, 440.
- 13 S. McN. Sieburth and C.-H. Lin, J. Org. Chem., 1994, 59, 3597.
- N. C. Yang and J. Libman, J. Am. Chem. Soc., 1972, 94, 9228;
  P. E. Eaton and U. R. Chakraborty, J. Am. Chem. Soc., 1978, 100, 3634;
  L. A. Paquette, C. W. Doecke and G. Klein, J. Am. Chem. Soc., 1979, 101, 7599;
  Y. Tobe, F. Hirata, K. Nishida, H. Fujita, K. Kimura and Y. Odaira, J. Chem. Soc., Chem. Commun., 1981, 786.
- 15 N. L. Allinger, Y. H. Yuh and J.-H. Lii, J. Am. Chem. Soc., 1989, 111, 8551.

Received, 14th June 1996; Com. 6/04193K