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

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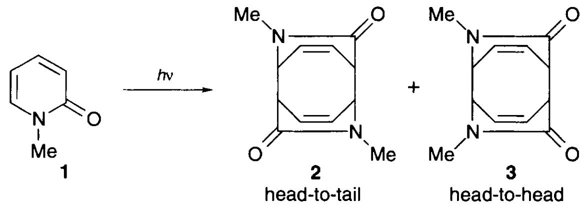
Symmetric 3,3′-attachment of a three-atom chain between two pyridones overrides the head-to-tail regioselectivity found in intermolecular photodimerization reactions and gives a nearly quantitative yield of the head-to-head [4 + 4] cycloadduct containing contiguous quaternary centres.

Photodimerization of 2-pyridones is an efficient [4 + 4] cycloaddition reaction characterized by high regioselectivity and modest stereoselectivity.[1,2] Despite more than thirty five years of study,[3] 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).[1] In other solvents, such as ethanol and benzene, only the head-to-tail products **2** were isolated.[4]

In our studies of intramolecular [4 + 4] photocycloadditions[2] 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.[2d] 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.[5]

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.[6] 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 alcohol **9** under phase-transfer conditions[7] to produce photosubstrate **5** in 85% yield.‡



solvent:			
benzene	100	:	0
ethanol	100	:	0
water	89	:	11

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

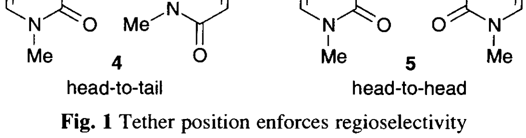
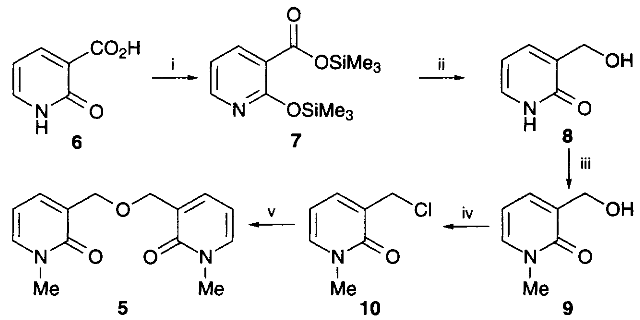


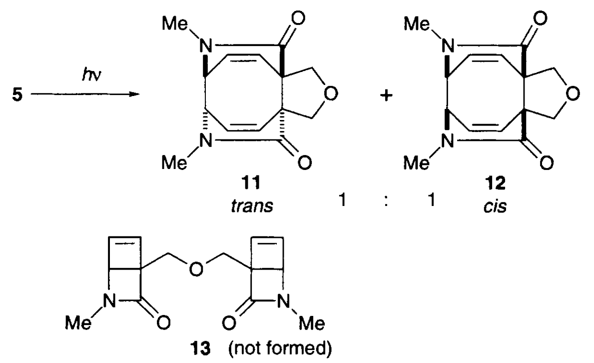
Fig. 1 Tether position enforces regioselectivity

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.[1,8,9] 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‡ of **11** and **12** ruled out the presence of β-lactams and confirmed that cycloaddition remained the exclusive path.

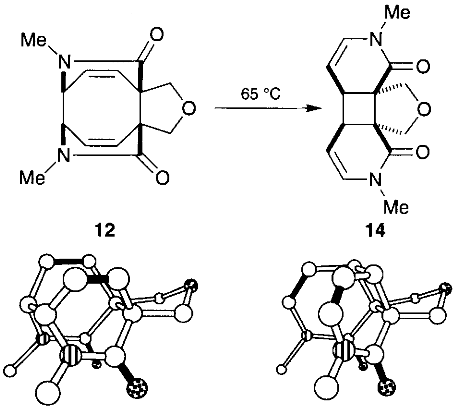
Additional supporting evidence for structures **11** and **12**, as well as identification of the *cis* isomer, was derived from heating a methanol solution of the mixture to reflux for 3 h



Scheme 2 Synthesis of photosubstrate **5**. *Reagents*: i, HMDS; ii, DIBAL; iii, MeI, K_2CO_3, MeOH; iv, $SOCl_2$; **9**, $BnNEt_3^+Cl^-$, 40% NaOH.



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



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.[14]

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.

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Footnotes

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‡ All new compounds were fully characterized. *Selected data* for **9**: mp 83 °C; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 162.7, 136.9, 135.8, 131.6, 106.1, 62.1, 37.4; IR (neat) 1648 cm^{-1}. For **5**: mp 152–153 °C; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 161.8, 136.7, 135.9, 129.6, 105.9, 68.1, 37.6; IR (KBr) 1654 cm^{-1}. For **11**: mp 164–165 °C; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 172.3, 137.5, 131.4, 74.4, 64.0, 61.3, 35.9; IR (KBr) 1651 cm^{-1}. For **12**: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 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); ^{13}C NMR ($CDCl_3$) δ 172.7, 136.2, 134.9, 74.4, 66.5, 62.3, 35.8; IR (KBr) 1662 cm^{-1}. For **14**: mp 157–159 °C; ^{1}H NMR ($CDCl_3$) 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 ($CDCl_3$) δ 164.9, 130.6, 102.4, 76.7, 59.7, 41.3, 34.9; IR (KBr) 1657 cm^{-1}.

§ 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^{-1} (74.7, 75.5 and 58.9 kcal mol^{-1}), respectively. See refs. 13 and 14.

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