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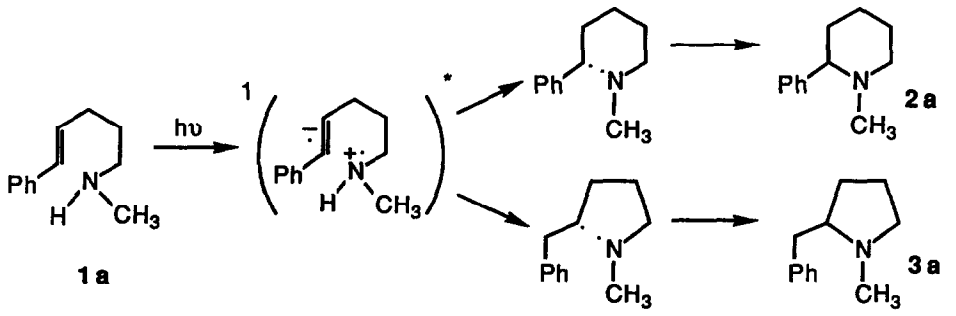
INTRAMOLECULAR PHOTOCHEMICAL REACTIONS OF N-ALKYL-5-PHENYL-4-PENTEN-1-AMINES

Frederick D. Lewis* and G. Dasharatha Reddy
Department of Chemistry, Northwestern University, Evanston, IL 60208 USA

Summary: Irradiation of N-alkyl-5-phenyl-4-penten-1-amines results in the formation of intramolecular styrene-amine adducts and disproportionation products. Increasing the bulk of the N-alkyl group increases the regioselectivity of N-H transfer favoring the formation of piperidine vs. pyrrolidine products and favors disproportionation vs. cyclization.

Intramolecular photochemical alkene-amine additions are attracting increasing attention as a method for the preparation of nitrogen heterocycles[1]. We recently reported that the irradiation of ω-styrylaminoalkanes results in efficient intramolecular addition.[2] For example, irradiation of *cis*- or *trans*-N-methyl-5-phenyl-4-penten-1-amine (**1a**) results in the formation of a ca. 2/1 ratio of regioisomeric adducts **2a** and **3a** with isolated yields of > 60% (eq 1). Variation in the length of the polymethylene chain connecting the styryl and amino groups from 1 to 5 permitted the photochemical synthesis of cyclic amines of ring size ranging from 4 to 8. In addition, ^{1}H NMR analysis of the adduct **2a** obtained using the N-deuterated amine *trans*-**1a**-N-d established that N-D addition to styrene is a stereospecific syn process. In order to further explore the potential utility of intramolecular styrene-amine addition for the stereocontrolled synthesis of cyclic amines, we have investigated the effect of increasing the bulk of the N-alkyl group. In view of our proposed mechanism (eq 1), increased bulk might be expected to affect (a) the rate constant for intramolecular electron transfer quenching, (b) the regioselectivity of N-H transfer, and (c) the behavior of the resulting biradical intermediates.

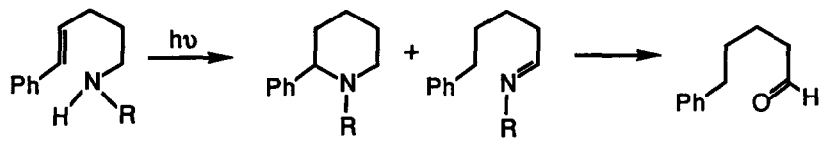


(1)

The *trans*-N-alkyl-5-phenyl-4-penten-1-amines **1a-c** were prepared via the reaction of *trans*-5-phenyl-4-pentenoic acid with the appropriate primary amine, followed by reduction of the resulting amide with $LiAlH_4$. The singlet lifetimes of **1a-c** as determined by single photon counting are all significantly shorter (< 0.5 ns) than that of *trans*-1-phenylpropene (11.6 ns).[3] Thus increasing the

size of the N-alkyl group does not decrease the rate constant for intramolecular electron transfer quenching. This result is in accord with the results of intermolecular quenching of singlet *trans*-stilbene by tertiary amines.[4]

Irradiation of the N-isopropylamine **1b** (0.01M) in acetonitrile after purging with dry nitrogen gas for 15 minutes in a Rayonet reactor fitted with RPR 3000 lamps (>95% conversion) followed by column chromatography results in the formation of N-isopropyl-2-phenylpiperidine (**2b**, 65%) and 5-phenylpentanal (15%).[5] GC-MS analysis of the irradiated solution prior to chromatography indicates that the imine **4b** is a primary product of the photochemical reaction and undergoes hydrolysis to yield the aldehyde **5** (eq 2). No evidence was obtained by GC-MS for the formation of N-isopropyl-2-benzylpyrrolidine. Irradiation of the N-t-butylamine **1c** followed by hydrolysis results in essentially quantitative formation of the aldehyde **5**. No evidence was obtained by GC-MS for the formation of either piperidine or pyrrolidine products from **1c**.



(2)

1b,c **2b** **4b,c** **5**

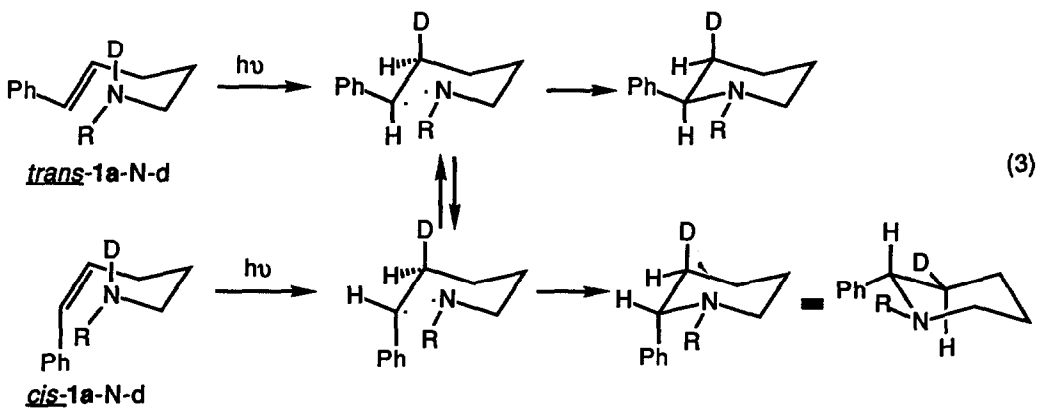
b: R = i-Pr
c: R = t-Bu

The failure to obtain pyrrolidine products from **1b** or **1c** might reflect either regioselective N-H transfer to the β-carbon or selective disproportionation of the biradical intermediate formed upon N-H transfer to the α-carbon. In order to distinguish between these possibilities, the aldehyde **5** obtained from the irradiation of **1c**-N-d was analyzed for deuterium content (>95% based upon GC/MS analysis) and location (>90% at C-4 based upon ^{13}C NMR analysis). Thus the formation of **5** from **1c**-N-d occurs via regioselective transfer of N-D to the β-carbon. Furthermore, when **1c**-N-d is recovered after ca. 50% conversion to products and analyzed for deuterium content and location by GC/MS and ^{1}H NMR, no H-D exchange of the vinyl protons can be detected. Thus the initially formed biradical intermediates either do not undergo disproportionation to yield starting material or do so in stereospecific fashion.

The results of product formation studies for styryl amines **1b** and **1c** indicate that both the regioselectivity of intramolecular N-H transfer and the behavior of the resulting biradical intermediates are dependent upon the bulk of the N-alkyl group. We previously reported that the regioselectivity of N-H transfer is dependent upon the length of the polymethylene chain separating the styryl and amino groups.[2] Bulky N-alkyl groups, like both short and long chain lengths, favor the formation of the thermodynamically more stable benzyl radical, which is also the predominant product of intermolecular styrene-secondary amine addition. The 1,6-biradical intermediates formed from **1b** and **1c** undergo either cyclization to yield a piperidine or disproportionation to yield

an imine (eq 2). Increasing the bulk of the alkyl group should result in increased non-bonded repulsion in the transition state for cyclization but not for disproportionation, in accord with the observed dependence of the product ratios upon the bulk of the N-alkyl group. Previous studies of intramolecular phenanthrene-amine additions by Sugimoto, et al.[6] established that bulky N-alkyl groups do not hinder addition in cases where disproportionation of the intermediate 1,6-biradical cannot occur.

The formation of both cyclization and disproportionation products via a common 1,6-biradical intermediate requires biradical lifetimes sufficiently long to allow rotational equilibration. This result in turn requires that the stereospecific syn N-H addition in *trans*-**1a**-N-d also occurs via a rotationally equilibrated biradical intermediate which cyclizes selectively to yield the syn adduct (eq 3). In order to test this hypothesis, the irradiation of *cis*-**1a**-N-d was investigated. Fortuitously, cis, trans isomerization does not compete effectively with cyclization and thus the piperidine product **2a** is not contaminated with the product from *trans*-**1a**-N-d. ^{1}H NMR analysis of the piperidine product from *cis*-**1a**-N-d indicates that it is a ca. 3:1 mixture of diastereomers, the major product being the same as that obtained from *trans*-**1a**-N-d. This result confirms that rotational equilibration of the biradical intermediate is indeed faster than cyclization. Preferential formation of the diastereomer in which D and Ph are cis presumably reflects a lower energy for the transition state leading to its formation.



(3)

The results of this investigation serve to establish several important features of the intramolecular photochemical styrene-amine addition reaction. Intramolecular addition via a 1,6-diradical intermediate to yield piperidines is the major photoprocess for styrylamines with methyl (**1a**) and isopropyl (**1b**) N-alkyl groups, while disproportionation to the imine is the major process for the N-t-butylamine (**1c**). Pyrrolidine formation occurs only for the N-methyl amine (**1a**). Both the competition between piperidine and imine formation and the stereochemistry of 1,6-diradical cyclization are determined by the relative transition state energies of rotationally equilibrated

biradical intermediates. Based on these results it may be possible to achieve facial selectivity in the addition reactions of styrylamines with chiral secondary N-alkyl groups.

References and Notes

1. (a) Xu, W.; Jeon, Y. T.; Hasegawa, E.; Yoon, U. C.; Mariano, P. S. *J.Am.Chem. Soc.* **1989,** *111,* 406. (b) Aoyama, H.; Arata, Y.; Omote, Y. *J.Chem.Soc.,Chem.Commun.* **1985,** 1381.
2. Lewis, F. D.; Reddy, G. D.; Schneider, S.; Gahr, M. *J.Am.Chem.Soc.* **1989,** *111,* 6465.
3. Singlet lifetimes determined for 10^{-4} M styrenes in nitrogen-purged cyclohexane solution using a PTI LS-1 fluorescence lifetime apparatus.
4. Lewis, F. D.; Ho, T.-I.; Simpson, J. T. *J.Org.Chem.* **1981**, *46,* 1077.
5. **2a:** ^{1}H-NMR ($CDCl_3$, TMS): δ 7.2-7.4 (m, 5H), 3.04 (bd, 1H), 2.75 (dd, 1H), 2.1 (m, 1H),1.99 (s, 3H), 1.8 (m, 1H), 1.7 (m, 3H), 1.6 (m, 4H), 1.35 (m, 1H); ^{13}C-NMR: δ 144.8 (s), 128.7 (d), 127.4 (d), 126.9 (d), 71.1 (d), 57.6 (t), 44.5 (q), 35.9 (t), 26.2 (t), 25.0 (t). M.S (m/z): 175 (100), 91, 57, 44; HRMS: Calcd.for $C_{12}H_{17}N$:175.1362; Found: 175.1353; **3a:** ^{1}H-NMR ($CDCl_3$): δ 7.3 (m, 5H), 3.1 (m, 3H), 2.6-2.1 (m, 3H), 2.33 (s, 3H), 1.6 (m, 4H): ^{13}C-NMR: δ 140.0 (s), 129.1 (d), 128.1 (d), 125.9 (d), 67.8 (d), 57.4 (t), 40.7 (q,t), 30.9 (t), 21.7 (t): HRMS: Found 175.1349: **2b**: ^{1}H-NMR ($CDCl_3$): δ 7.1-7.4 (m, 5H), 3.3 (dd, 1H), 2.9 (m, 1H), 2.8 (sep, 1H), 2.2 (dt, 1H), 1.5-1.8 (m, 5H), 1.3 (m, 1H), 0.97 (d, 3H),0.75 (d, 3H): ^{13}C-NMR δ 144.0 (s), 128.0 (d), 127.1 (d), 126.3 (d), 47.9 (d), 43.8 (d), 36.9 (t), 36.0 (t), 25.2 (t), 21.0 (q), 11.7 (q): M.S (m/e): 203 (M^+), 188 (100), 126 (58): **4b**: M.S (m/e): 203 (M+), 112, 91, 70: **4c**: M.S (m/e): 217 (M^+) 202 (100), 160, 140, 91, 84: **5**: ^{1}H-NMR (CDCl3): δ 9.7 (t, 3H), 7.1-7.3 (m, 5H), 2.6 (t, 2H), 2.42 (t, 2H), 1.6 (m, 4H): ^{13}C-NMR: δ 202.4 (s), 141.8 (s), 128.3 (d), 125.8 (d), 43.7 (t), 35.6 (t), 30.8 (t), 21.7 (t): M.S (m/e): 162 (M^+), 91 (100): IR (chloroform): 1730 (carb. stretch) cm^{-1}.
6. Sugimoto, A.; Sumida, N.; Tamai, N.; Inoue, H.; Otsuji, Y. *Bull.Chem.Soc.Jpn.* **1981,** *54,* 3500.

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