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Photochemical transformation of a 1,2-dihydropyridin-3-one: an original tandem retro-[4+2]/[2+2] cycloaddition process

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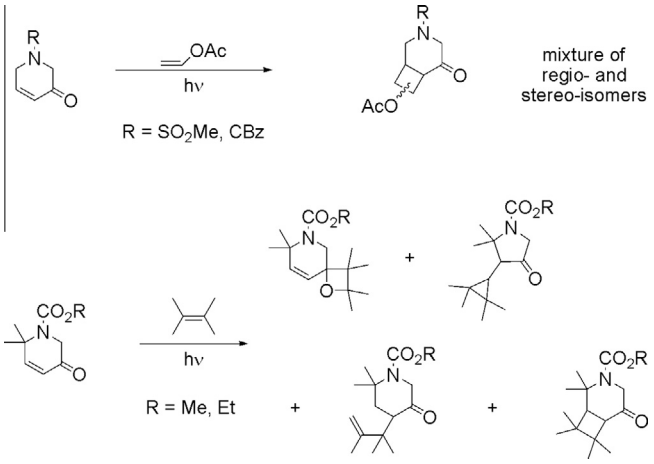
ABSTRACT

The UV irradiation of *N*-benzyl-2-phenyl-1,2-dihydropyridin-3-one furnished *trans*-1-benzyl-4-phenyl-3-vinylazetidin-2-one, a structural isomer, as the main product. A novel tandem mechanism involving a [4+2] photocycloreversion followed by a Staudinger cycloaddition reaction is proposed, and is supported with the trapping of the purported vinylketene intermediate by other imines. This process predominates in the presence of ethylene, precluding the formation of an intermolecular [2+2] cyclobutane adduct.

Dihydropyridin-2-ones and dihydropyridin-4-ones have occupied a significant place in heterocyclic chemistry for many years.[1] Although less studied, their structural isomers of the dihydropyridin-3-one family are also useful intermediates in the synthesis of natural products.[2] As enones, they are potential partners for photochemical [2+2] cycloaddition reaction with alkenes,[3] and the presence of the heteroatom is an asset for targeting diversely-functional molecular systems through such reactions.[4] In the literature however, there are only two reports of photocycloaddition reactions involving dihydropyridin-3-ones (Scheme 1). Hanaoka irradiated a selection of *N*-functionalized derivatives with vinyl acetate, and isolated the corresponding cyclobutane adducts as mixtures of stereo- and regio-isomers.[5] Margaretha studied the photochemical reaction of a carbamate derivative of 6,6-dimethyl dihydropyridin-3-one with tetramethylethylene, and found that this sterically challenging reaction provided the cyclobutane adduct in low yield, accompanied by several other products, resulting from rearrangements of the biradical intermediate (Scheme 1).[6]

Recently, we developed an efficient synthesis of 2-substituted dihydropyridin-3-ones from α-aminoacids.[7] We decided to investigate the photochemical behavior of such materials when irradiated in the presence of an alkene.

A selection of N-substituted 2-phenyldihydropyridin-3-ones was prepared from commercially available (*R*)-phenylglycine **1** (Scheme 2). Esterification then N-allylation gave intermediate **2**, which was then treated with the appropriate electrophile to prepare tosylamide **3a**, benzyl and *t*-butyl carbamates **3b** and **3c**, and benzylamine **3d**. Cyclopropanation of the *N*-allyl esters **3a–d** using Kulinkovich conditions[8] gave the corresponding 3-azabicyclo[3.1.0]hexanols **4a–d** as non-separated mixtures of diastereomers. Finally, Saegusa oxidation[9] provided the target 3-dihydropyridinones **5a–d** in reasonable overall yields (Scheme 2).



Scheme 1.

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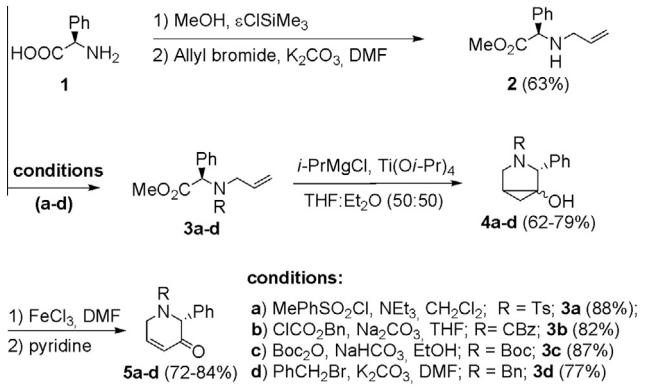
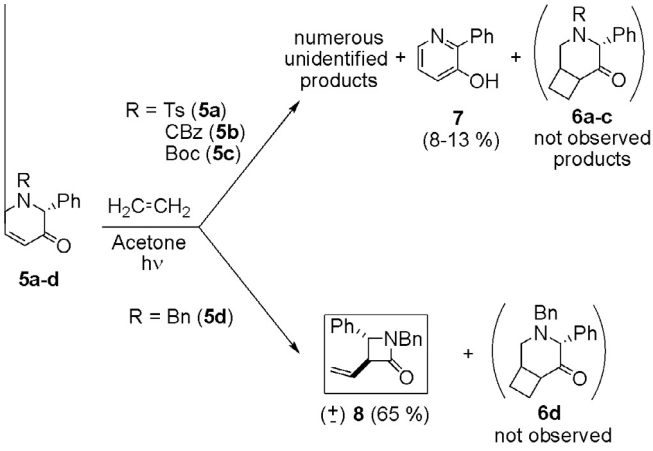


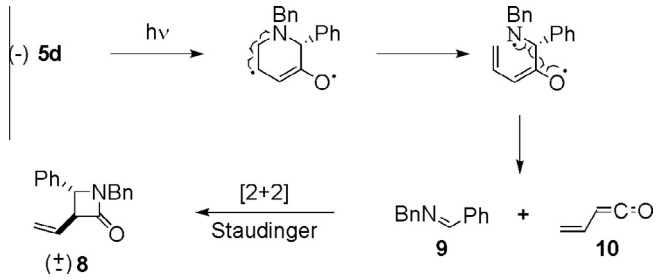
Scheme 2.

Each of the 3-dihydropyridinones **5a**–**d** was irradiated in solution in acetone for 3 h (400 W Hg lamp, Pyrex filter) while ethylene was bubbled through the mixture. After the reaction time, the solvent was evaporated and the crude mixture was examined by tlc and NMR spectroscopy. From compounds **5a**–**c**, a plethora of products was formed, and the anticipated cyclobutane adducts **6a**–**c** were not in evidence. After preparative chromatography, 2-phenyl pyridine-3-ol **7** was isolated in low yield (around 10%), evidently the result of nitrogen-function cleavage followed by aromatization. This product had previously been encountered in the palladium catalyzed hydrogenation of dihydropyridinone **5d**.[2] Use of other solvents (acetonitrile, dichloromethane) or a different alkene (vinyl acetate instead of ethylene) did not simplify the reaction profile, and the reaction mixtures remained largely intractable. In contrast, when 3-dihydropyridinone **5d** was irradiated in acetone solution as described above, one major product was obtained. Analysis of spectroscopic data led us to deduce that this product was not the anticipated cyclobutane adduct 6d (which we could not detect at all), but was in fact the *trans* 2-azetidinone (β-lactam) **8**, isolated in 65% yield (Scheme 3).

To explain the formation of lactam **8**, we postulate that the excitation of the enone chromophore is followed by a vinylogous homolytic cleavage. The biradical intermediate then fragments to give two discreet species, the imine **9** and vinylketene **10**. A related two-step photochemically-induced formal retro-[4+2] process was suggested by Zimmermann to explain ring fission of 4,4-diphenyldihydropyridin-2-ones,[10] and a similar ring opening process was suggested by Margaretha to occur during the irradiation of dihydrothiin-3-one *S*-oxides.[11] The subsequent reaction pathways deviated in the above-cited studies, but here it seems likely that



Scheme 3.

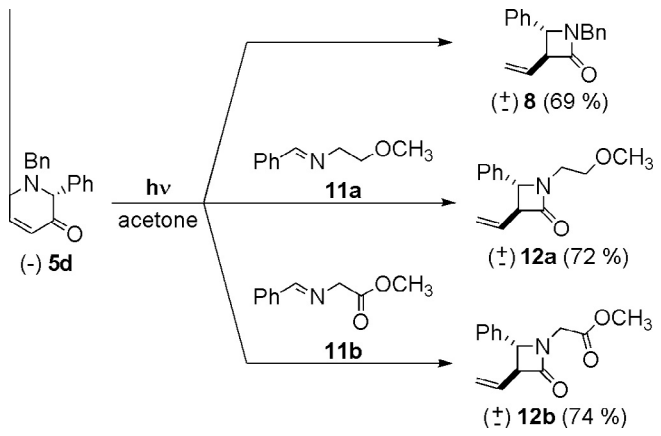


Scheme 4.

the two new products **9** and **10** should combine in a Staudinger cycloaddition reaction to afford the corresponding β-lactam.[12] The exclusively *trans* stereochemistry of **8** was attested by NMR spectroscopy, notably the observation of a coupling constant of about 2 Hz (J $H_{(C3)}$–$H_{(C4)}$) and NOESY correlations between $H_{(C4)}$ and $H_{(CH=CH2)}$, and is consistent with the results of Staudinger reactions of imines and ketenes conducted in photochemical conditions reported independently by Podlech[13] and Xu.[14] Compound **8** was optically inactive, consistent with the suggested mechanism for its formation (Scheme 4).

The proposed mechanism for the formation of **8** suggests that the presence of ethylene is superfluous, so we irradiated an acetone solution containing only **5d** as solute for 3 h. As anticipated, work-up provided **8** in 69% isolated yield. A further postulate based on the mechanism is that if an imine other than **9** were present in the reaction medium it should be able to trap the proposed vinylketene intermediate. We therefore irradiated an acetone solution of **5d** in the presence of 10 equiv of either *N*-benzylidene-2-methoxyethanamine[15] (**11a**) or methyl *N*-benzylideneglycinate[16] (**11b**) for 3 h. As predicted, a new *trans*-disubstituted β-lactam (**12a** or **12b**, respectively) was obtained as the major product in each case (Scheme 5). These observations are in agreement with the mechanism suggested in Scheme 4.

The intramolecular [2+2] cycloaddition of 2-pyridones to give bicyclic β-lactams was first discovered by Corey and Streith,[17] and these strained intermediates have been used to make *cis*-divinyl β-lactams through ring-opening cross metathesis.[18] Photorearrangement of dihydrothiin-3-ones to thietan-3-ones has been described, again via a strained bicyclic intermediate (a sulfuranyl-alkyl biradical).[19] However, the photoisomerization of dihydropyridin-3-ones via the tandem [4+2]-cycloreversion/[2+2] cycloaddition process described here is, to the best of our knowledge, unprecedented for heterocyclic systems.[20]



Scheme 5.

Acknowledgments

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References and notes

1. (a) Quirion, J.-C.; Leclerc, E.; Jubault, P. *Sci. Synth.* **2007**, *33*, 601–628; (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156.
2. Jida, M.; Ollivier, J. *Eur. J. Org. Chem.* **2008**, 4041–4049. and references cited therein..
3. Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297–588.
4. (a) Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000–1045; (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052–1103.
5. (a) Imanishi, M.; Wada, T.; Inoue, Y.; Hanaoka, M. *Heterocycles* **1981**, *16*, 2133–2136; (b) Imanishi, T.; Inoue, M.; Wada, Y.; Hanaoka, M. *Chem. Pharm. Bull.* **1983**, *31*, 1235–1242.
6. (a) Jeandon, C.; Constien, R.; Sinnwell, V.; Margaretha, P. *Helv. Chim. Acta* **1998**, *81*, 303–306; (b) Constien, R.; Kisilovski, B.; Meyer, L.; Margaretha, P. *Russ. Chem. Bull.* **1999**, *48*, 510–512.
7. Jida, M.; Guillot, R.; Ollivier, J. *Tetrahedron Lett.* **2007**, *48*, 8765–8767.
8. Kulinkovich, O. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1065–1086.
9. Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth. Coll.* **1988**, *6*, 327–333.
10. Zimmerman, H. E.; Mitkin, O. D. *J. Am. Chem. Soc.* **2006**, *128*, 12743–12749.
11. Kowalewski, R.; Margaretha, P. *Helv. Chim. Acta* **1993**, *76*, 1251–1257.
12. (a) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51–123; (b) Xu, J. *Arkivoc* **2009**, *ix*, 21–44.
13. Maier, T. C.; Frey, W.; Podlech, J. *Eur. J. Org.* **2002**, 2686–2689. and references therein.
14. Liang, Y.; Jiao, L.; Xu, J. *J. Org. Chem.* **2005**, *70*, 334–337.
15. Mangeney, P.; Tejeroo, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255–257.
16. Gemma, L. T.; Spandl, R. J.; Glandsdorp, F. G.; Welch, M.; Bender, A.; Cockfield, J.; Lindsay, J. A.; Bryant, C.; Brown, D. F. J.; Loiseleur, O.; Rudyk, H.; Ladlow, M.; Spring, D. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 2808–2812.
17. Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950–951.
18. Adamo, A. F. A.; Disetti, P.; Piras, L. *Tetrahedron Lett.* **2009**, *50*, 8765–8767.
19. Er, E.; Margaretha, P. *Helv. Chim. Acta* **1992**, *75*, 2265–2269.
20. *Experimental procedure:* A solution of *N*-benzyl-1,2-dihydro-2-phenylpyridin-3(*6H*)-one **5d** (1 mmol) and, where appropriate, imine **11a** or **11b** (10 mmol) in acetone (250 mL) was placed in an annular photochemical reactor fitted with a Pyrex filter. The solution was deoxygenated by the passage of a stream of argon for 30 min, then irradiated using a 400 W Hg lamp. Progress of the reaction was monitored by tlc until the disappearance of the starting dihydropyridinone (~3 h). The solvent was then evaporated and the residue was taken up in 100 mL of ether. This solution was washed with 1 M HCl (3 × 10 mL), 10% aq $NaHSO_3$ solution (10 mL), 10% aq Na_2CO_3 solution (10 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc; 90:10) to afford the *trans* β-lactam. *Selected data:* Compound **8**, *trans*-1-benzyl-4-phenyl-3-vinylazetidin-2-one. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.15 (m, 10H), 5.94 (ddd, J = 17.5, 10.5, 8.0 Hz, 1H), 5.31 (dt, J = 17.5, 1.2 Hz, 1H), 5.25 (dt, J = 10.5, 1.2 Hz, 1H), 4.35 (AB system, δνAB = 273 Hz, J = 15.0 Hz, 2H), 4.22 (d, J = 2.2 Hz, 1H), 3.70 (dd, J = 8.0, 2.2 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.0, 137.1, 135.4, 130.1, 129.0, 128.7, 128.3, 128.3, 127.7, 126.4, 119.1, 63.9, 60.6, 44.5. FT-IR (NaCl, cm^{-1}) 3086, 3063, 2917, 1757, 1456. HRMS (ESI) m/z Calcd for $C_{18}H_{17}NNaO$: 286.1202. Found: 286.1217. Compound **12a**, *trans*-1-(2-methoxyethyl)-4-phenyl-3-vinylazetidi-2-one. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 6.02 (ddd, J = 17.2, 10.2, 8.0 Hz, 1H), 5.33 (dt, J = 17.2, 1.1 Hz, 1H), 5.29 (dt, J = 10.2, 1.1 Hz, 1H), 4.48 (d, J = 2.25 Hz, 1H), 3.69 (m, 2H), 3.47 (m, 2H), 3.27 (s, 3H), 3.08 (ddd, J = 14.4, 7.0, 4.2 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.4, 137.8, 131.1, 128.9, 128.4, 126.3, 119.0, 69.7, 64.1, 58.3, 40.1.δ FT-IR (NaCl, cm^{-1}) 3031, 2925, 1756, 1638, 1495. HRMS (ESI) m/z Calcd for $C_{14}H_{17}NNaO_2$: 254.1157. Found: 254.1151. Compound **12b**, *trans*-methyl 2-(2-oxo-4-phenyl-3-vinylcyclobutyl) acetate. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.44–7.31 (m, 5 H), 6.04 (ddd, J = 17.1, 10.4, 8.1 Hz, 1H), 5.35 (d, J = 17.1, 1H), 5.31 (d, J = 10.4 Hz, 1H), 4.64 (d, J = 2.3 Hz, 1H,), 3.96 (AB system, δνAB = 233 Hz, J = 18.1 Hz, 2H), 3.80–3.52 (m, 1H), 3.73 (s, 3H). ^{13}C ($CDCl_3$, 63 MHz) δ 168.3, 168.2, 136.7, 130.5, 128.9, 128.6, 126.2, 119.4, 64.5, 61.8, 52.1, 41.2. FT-IR (NaCl, cm^{-1}) 3031, 2953, 1762, 1742, 1639, 1495. HRMS (ESI) m/z Calcd for $C_{14}H_{15}NNaO_3$: 268.0950. Found: 268.0941.