

A NOVEL PHOTOCHEMICAL SYNTHESIS OF PYRROLES FROM β -KETOVINYLOGOUS AMIDES

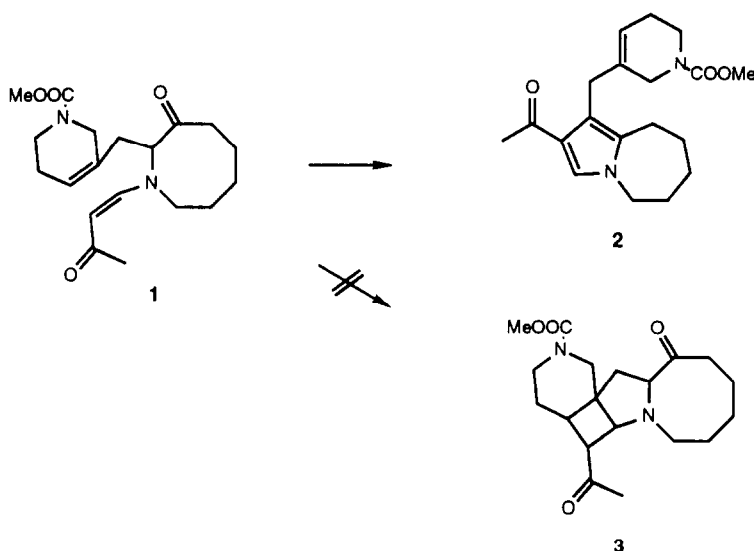
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Summary: Irradiation of β -ketovinylogous amides leads to the formation of 3-acylpyrroles. A mechanistic rationale is offered which involves the recombination of a photochemically generated biradical, followed by transannular condensation to give the observed pyrrole product.

The inter- and intramolecular [2+2]-photocycloaddition reaction of vinylogous amides and imides is a useful process in organic synthesis.³ We have recently reported that the intramolecular photocycloaddition of vinylogous amides and the subsequent facile retro-Mannich fragmentation can be coupled to a Mannich ring closure to give an efficient process for the construction of perhydroindoles with a variety of substitution patterns.⁴ In this Letter, we report a novel photochemical transformation of vinylogous amides, in which irradiation of a β -ketovinylogous amide leads not to the expected [2+2] photoadduct, but instead to the formation of a 3-acylpyrrole.

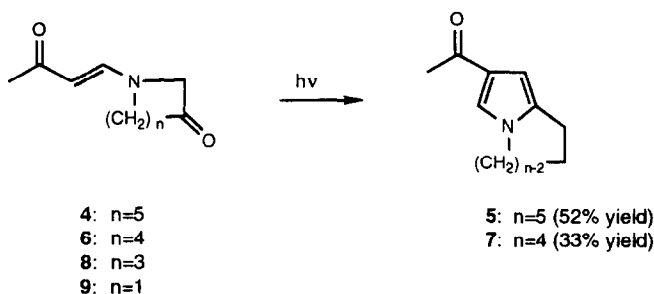
Scheme I



Irradiation of vinylogous amide 1 (0.05 mM in acetonitrile, 25°C, 450W mercury lamp w/Pyrex filter) led not to the expected [2+2] product 3, but instead resulted in the formation of the acylpyrrole product 2 in 25 % yield.⁵ The spectator role of the tetrahydropyridine alkene in 1 was clearly established by irradiation of 4 to give the analogous pyrrole 5 (Scheme II).

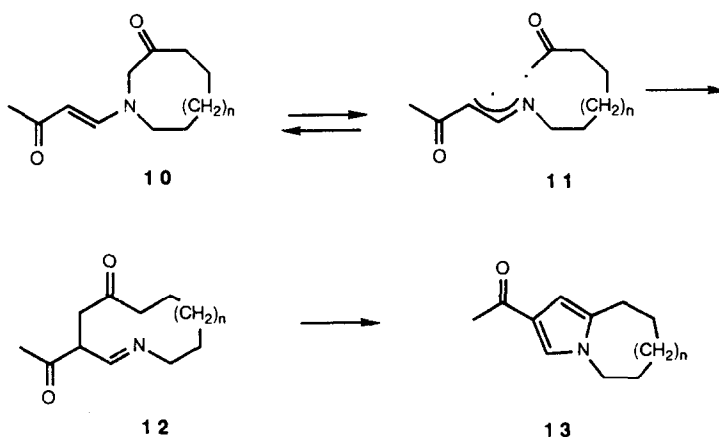
The scope and limitations of this novel photochemical transformation were then examined. Irradiation of the seven-membered ring substrate **6** led to the formation of the analogous product **7**, although the rate of the reaction was ca. 20 times slower than the rate of formation of **5**. The longer irradiation time that is required for the photocyclization of **6** is presumably responsible for the lower yield in this reaction, as the pyrrole product **7** undergoes substantial decomposition on prolonged irradiation.⁶ Subjection of the six-membered ring photosubstrate **8** to the same reaction conditions led only to decomposition of **8** without formation of any identifiable products. Interestingly, irradiation of **9**, the four-membered ring substrate, gave only recovered starting material on prolonged irradiation.

Scheme II

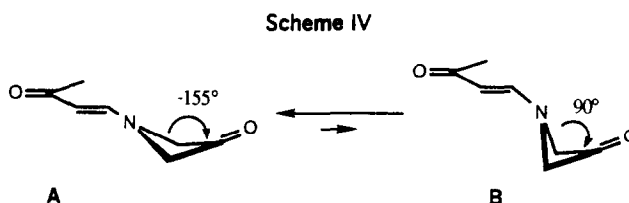


A mechanism that is consistent with these results is outlined in Scheme III. Excitation of the vinylogous amide chromophore **10** leads to bond homolysis to form the stabilized diradical **11**, which can then undergo ring closure to regenerate the starting material or, via cyclization at the other terminus of the aza-allylic radical, to the ring expanded ketoimine, **12**. The imine can then undergo a ground state transannular cyclization to give, after dehydration, the observed pyrrole product, **13**.

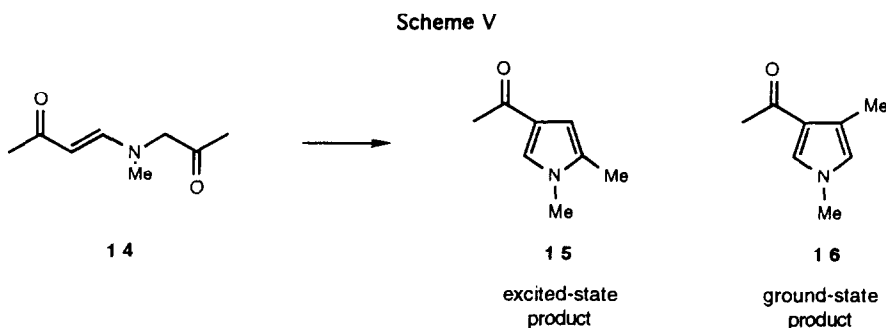
Scheme III



The marked difference in the photoreactivities of **4**, **6**, **8**, and **9** can be explained by a combination of the relative rates of diradical recombination and stereoelectronic effects. The recombination rates of diradicals to form eight- and nine-membered rings are known to be much slower than the corresponding reactions to form other ring sizes.⁷ In the case of **4**, the ring expansion from an eight- to a ten-membered ring should be favorable, relative to the corresponding reaction of the seven-membered ring substrate **6** which undergoes ring expansion to give a nine-membered ring ketoimine. The six-membered ring photosubstrate, **8**, which would expand from a six- to an eight-membered ring, would be expected to react much more slowly than either **4** or **6**, and, in the event, only photodegradation is observed on irradiation of **8**. The relative photostability of **9** can be attributed to stereoelectronic factors. For maximum bond overlap and consequently maximum radical stabilization, the bond undergoing homolysis in the first step of the mechanism outlined in Scheme III should be approximately perpendicular to the ketone carbonyl. Such a geometry would be quite difficult to achieve in a four-membered ring as shown in conformation B (Scheme IV), but would be easily attained in a seven- or eight-membered ring.



This photochemical synthesis of pyrroles was next examined in an acyclic system, in which the first bond homolysis would necessarily generate two separate radical species (Scheme V). It was anticipated that the yield of pyrrole formation, which must now compete with dissociation of the initially formed radical pair from the solvent cage, would be lower in this system. In the event, irradiation of **14**, under conditions identical to those described above, led to the formation of pyrrole **15** in a modest 16% yield.



While the yields remain to be optimized, this excited state reaction nicely complements the better known Knorr synthesis of pyrroles, in which ground state cyclization of **14** leads to the formation of the isomeric pyrrole, **16**. Further study of this rearrangement from both mechanistic and synthetic standpoints is currently underway in our laboratories, and our results will be reported in due course.

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References

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- ² National Institutes of Health Predoctoral Trainee, University of Chicago (GM07151). Current address: Department of Chemistry, Yale University, New Haven, CT 06511.
- ³ For a recent review, see a) De Keukeleire, D. D.; He, S. H. *Chem. Rev.* **1993**, *93*, 359; b) Crimmins, M. *Chem. Rev.* **1988**, *88*, 1453. For examples of the utility of vinylogous amides and imides, see c) Tamura, Y.; Ishibashi, H.; Jirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40*, 2702; d) Schell, F.; Cook, P. *J. Org. Chem.* **1984**, *49*, 4067; e) Swindell, C.; deSolms, J.; Springer, J. *Tetrahedron Lett.* **1984**, *25*, 3797.
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- ⁵ All new compounds gave satisfactory ¹H and ¹³C NMR, IR and MS data. Pyrrole **5** crystallized in the monoclinic space group P2₁/n (systematic absences 0k0: k=odd and h01:h+1=odd) with a=11.415(1); b=6.295(1), c=14.091(1)Å, β=101.32(1), V=992.8(3)Å³, Z=4 and d_{calc}=1.186 g/cm³. Spectral data for **5**: ¹H NMR: 7.14 (d, 1H, J=2.0 Hz), 6.29 (d, 1H, J=1.9 Hz), 3.93 (t, 2H, J=5.8 Hz), 2.68 (t, 2H, J=5.5Hz), 2.34 (s, 3H), 1.6-1.8 (m, 6H); ¹³C NMR: 193.3, 137.1, 126.5, 123.8, 107.1, 50.9, 30.8, 29.7, 28.1, 28.0, 26.8; IR (cm⁻¹, neat): 2850, 1650, 1520, 1440, 1385, 1205; UV (CH₃CN): 247 nm, ε=6700; 209 nm, ε=10350. High resolution mass spectrum calculated for C₁₁H₁₆NO (M+H): 178.1232; found, 178.1230.
- ⁶ Irradiation of **7** in acetonitrile for 4 h led to only a 40% yield of recovered pyrrole.
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