J|A|C|S
COMMUNICATIONS

The Intramolecular Photometathesis of Pyrroles

Luke D. Elliott,[†] Malcolm Berry,[‡] Andrew J. Orr-Ewing,[†] and Kevin I. Booker-Milburn*,[†]

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K., and Medicines Research Centre, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, U.K.

Received January 12, 2007; E-mail: k.booker-milburn@bristol.ac.uk

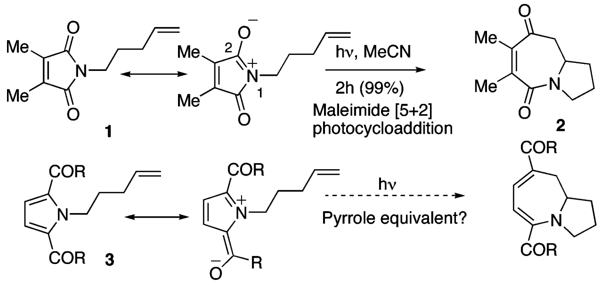
Over the last 40 years the photochemistry of benzene and its derivatives has been studied in great detail and is now well documented and understood. The synthetic potential of reactions such as arene meta photocycloaddition are well established and have been applied to notable effect in numerous complex natural product syntheses.[1] In contrast, the situation for many heteroaromatic systems is much less well developed.[2] For example, successful transformations involving pyrroles in the excited state are rare by comparison.[3] Previously reported reactions include the rearrangement[4] of 2-cyano pyrroles and one report of the direct [2+2] photocycloaddition of alkenes onto the 2,3-position of 1-methyl-2-acetylpyrrole.[5] Herein we report our findings in the area of pyrrole photochemistry which have resulted in the realization of a novel photometathesis sequence.

Previously we reported[6] that maleimides **1** undergo a formal [5+2] photocycloaddition sequence resulting in the synthetically useful production of bicyclic azepines **2** in a single operation (Scheme 1). The mechanism at the time of the present study was postulated to proceed via intramolecular [2+2] cycloaddition across the N1−C2 bond of the maleimide followed by ionic fragmentation of the resulting zwitterionic species.[7] We were intrigued to see if similar reactivity would be displayed by meso electronically related pyrrole derivatives (e.g., **3**), potentially broadening the scope of this [5+2] cycloaddition beyond the limitations imposed by the maleimide chromophore.

Several electron deficient disubstituted pyrroles were synthesized,[8] all of which contained the *N*-pentenyl chain for cycloaddition. Irradiation of these with a number of UV sources led to either recovered starting material or decomposition. In the case of the 2,4-disubstituted series, however, UV irradiation led to an unexpected but consistent reaction pathway. For example, irradiation of **4** in a Vycor immersion well with a 125 W medium-pressure Hg-lamp yielded a labile product identified as the enamine-enone **5**. This remarkable product appeared to be the result of metathesis of the pendent alkene with the C2−C3 bond of the pyrrole as indicated in Scheme 2.

In general, the reaction required electron withdrawing groups in the 2- and 4-positions of the pyrrole. Although the 4-position specifically required ketone/aldehyde substitution, ester/amide/nitrile were all tolerated in the 2-position (Table 1). In a number of examples it was possible to observe the formation and subsequently isolate a cyclobutane intermediate. For example, irradiation of the 2-amido pyrrole **6** (entry 5; R = CONHEt, R′ = Me, R″ = H) yielded the photometathesis product **7** (R = CONHEt, R′ = Me, R″ = H) and the cyclobutane **8** (R = CONHEt, R′ = Me, R″ = H), the structure of which was confirmed by X-ray crystallography (see Supporting Information). Specific short wavelength irradiation (methods B/C; entries 6 and 7) led to a predominance of the cyclobutane product, confirming it as the first formed intermediate in the whole sequence. Generally, yields of the photometathesis products in Vycor were maximized using a high power medium-pressure Hg source (125 W). The disadvantage of this was photodegradation of the products **7** on prolonged irradiation with short wavelength UV produced by this lamp. Although high mass balances (e.g., entry 6) were obtained using low-pressure Hg sources, conversion to **7** was incomplete even on prolonged irradiation times because of the wavelength dependence of the sequence (vide infra).

Scheme 1



Scheme 2. Intramolecular Photometathesis of a 2,4-Disubstituted Pyrrole

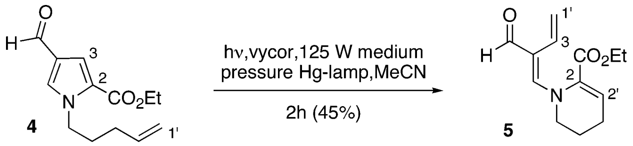
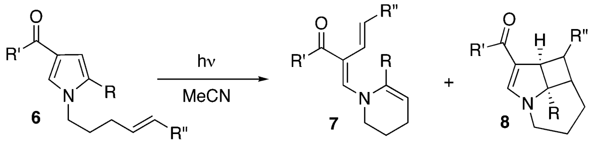


Table 1. Photometathesis of *N*-Pentenyl-2,4-disubstituted Pyrroles **6** Using Various UV Light Sources



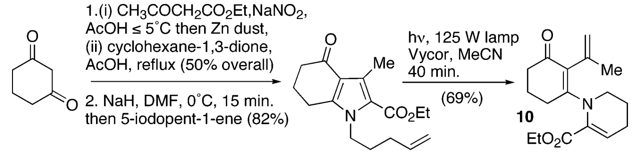
entry	R	R″	R′	t	method[a]	yield **7** (%)	yield **8** (%)
1	CO_2Et	H	H	3 h	A	45	
2	CO_2Et	H	Me	1.3 h	A	45	23
3	CO_2Et	H	CH_2Ph	1 h	A	20	
4	CO_2Et	H	CH_2Ph	40 min	A	12	24
5	CONHEt	H	Me	3 h	A	40	11
6	CONHEt	H	Me	25 h	B	34	47
7	CONHEt	H	Me	3 h	C	6	39
8	CN	H	Me	2 h	A	25	28
9	CN	H	Me	48 h	B		32
10	CONHEt	Me	Me	45 min	A	26[b]	38[b]
11	CONHEt	Me	Me	23 h	B		60[b]

[a] Method A: 125 W medium-pressure Hg-lamp, Vycor immersion well. Method B: 6 W low-pressure Hg-lamp, quartz immersion well. Method C: laser irradiation at 222 nm, quartz cuvette. [b] Based on recovered **6**.

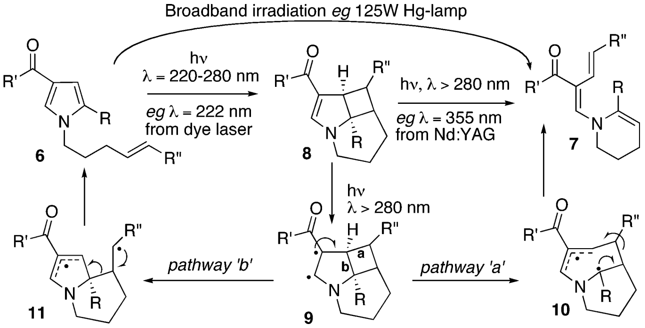
[†] University of Bristol.
[‡] GlaxoSmithKline.

10.1021/ja070254l CCC: $37.00

Scheme 3



Scheme 4. Proposed Mechanism for the Wavelength-Dependent Photometathesis of Pyrroles (R = CONHEt, R′ = Me, R″ = H)



As quantities of the thermally stable cyclobutane intermediate **8** (R = CONHEt, R′ = Me, R″ = H) were available from irradiations using low-pressure lamps we undertook a study to gain some insight into the likely mechanism of the photometathesis sequence. Significantly, it was found that the overall sequence proceeds via two discrete wavelength-dependent reactions which could be decoupled and studied by appropriate choice of monochromatic source. The fact that irradiation of **6** (R = CONHEt, R′ = Me, R″ = H) yields predominantly **8** (R = CONHEt, R′ = Me, R″ = H) at 222 nm (laser) and at 254 nm (low-pressure lamp) suggests that the strong UV absorption of ~250 nm exhibited for this pyrrole is the key region for excitation for the initial [2+2] cycloaddition. The cyclobutane **8** (R = CONHEt, R′ = Me, R″ = H) exhibits a strong absorption feature at 300−350 nm in the UV spectrum. It was found that irradiation of pure **8** (R = CONHEt, R′ = Me, R″ = H) with monochromatic 355 nm UV from a Nd:YAG laser gave equimolar amounts of the starting pyrrole **6** (R = CONHEt, R′ = Me, R″ = H) and photometathesis product **7** (R = CONHEt, R′ = Me, R″ = H).

A more elaborate example involving photometathesis of a fused pyrrole was realized by submitting cyclohexane-1,4-dione to a Knorr pyrrole synthesis followed by N-alkylation. Irradiation of the resulting pyrrole resulted in clean photometathesis to the complex enone-enamine **10** (Scheme 3).

On the basis of these above findings a general mechanism for the complete photometathesis sequence using broadband UV light is proposed in Scheme 4. Absorption of shortwave UV (220−280 nm) first results in excitation of the pyrrole nucleus in **6** engaging the initial [2+2] cycloaddition to **8**. Continued irradiation (>280 nm) likely results in the triplet diradical **9** (initially via n → π^* excitation of the enone C═O). This diradical then undergoes fragmentation to product **7** and back to starting pyrrole **6** via the respective pathways “a” and “b” as supported by laser irradiation at 355 nm. Under continuous irradiation with broadband UV, any pyrrole **6** regenerated from **8** is recycled to the photometathesis product. Laser irradiation of pure **7** (R = CONHEt, R′ = Me, R″ = H) at 355 nm showed no reaction, indicating that this final step is irreversible.

In summary a new photochemically mediated intramolecular metathesis sequence of pyrroles has been described. The reaction has been shown to proceed via two sequential wavelength-dependent reactions involving [2+2] cycloaddition at 220−280 nm followed by a *retro*-[2+2] of the resulting cyclobutane at wavelengths longer than this. Reversibility in cyclobutane formation is well documented, and in the context of metathesis there have been reports of photochemically mediated [2+2] followed by *thermally* mediated *retro*-[2+2].[9] However, to the best of our knowledge the present study represents the first example of a metathesis sequence where both steps are photochemically controlled. Notably these two discrete steps can be decoupled and studied by wavelength selection from tunable UV lasers.

Acknowledgment. We thank EPSRC (GR/S25593) and GSK for generous funding of this study and Keith N. Rosser for help with the lasers. A.J.O.E. thanks the Leverhulme Trust for the award of a Senior Research Fellowship.

Supporting Information Available: Experimental procedures and characterization data for pyrroles and photoproducts and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent highlight of arene phototchemistry see: Mattay, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 663.
(2) (a) Pérez-Ruiz, R.; Miranda, M. A.; Alle, R.; Meerholz, K.; Griesbeck, A. G. *Photochem. Photobiol. Sci.* **2006**, *5*, 51. (b) D’Auria, M.; Emanuele, L.; Racioppi, R. *J. Photochem. Photobiol., A* **2004**, *163*, 103.
(3) (a) Bellas, M.; Bryce-Smith, D; Gilbert, A. *Chem. Commun.* **1967**, 263. (b) Basaric, N.; Marinic, Z.; Sindler-Kulyk, M. *J. Org. Chem.* **2006**, *71*, 9382.
(4) (a) Hiraoka, A. *Chem. Commun*. **1970**, 1306. (b) Barltrop, J.; Day, A. C.; Moxon, P. D.; Ward, R. R. *J. Chem Soc., Chem. Commun*. **1975**, 786.
(5) Cantrell, T. S. *J. Chem. Soc., Chem. Commun.* **1972**, 155.
(6) Booker-Milburn, K. I.; Anson, C. E. A.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* **2001**, 1473.
(7) (a) Mazzocchi, P. H.; Bowen, M. J.; Narain, N. K. *J. Am. Chem. Soc.* **1977**, *99*, 7063. (b) Mazzocchi, P. H.; Minamikawa, S.; Bowen, M. J. *J. Org. Chem.* **1978**, *43*, 3079. (c) Mazzocchi, P. H.; Minamikawa, S.; Wilson, P. *J. Org. Chem.* **1979**, *44*, 1186. (d) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikawa, S. *J. Org. Chem.* **1983**, *48*, 2981.
(8) Substituted pyrroles used were known compounds synthesized by selective 4-acylation of 2-trichloroacetyl pyrrole. N-akylations were carried out on the pyrrole anions and 5-bromo-1-pentene or with 4-pentene-1-ol by Mitsunobu reaction.
(9) (a) Inaki, I. *CRC Handbook of Organic Photochemistry and Photobiology;* Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; p 104. (b) Kammermeier, S.; Herges, R. *Angew. Chem., Int. Ed.* **1996**, *35*, 417. (c) Wiberg, K. B.; Matturro, M.; Adams, R. *J. Am. Chem. Soc.* **1981**, *103*, 1600. (d) Camps, P.; Font-Bardia, M.; Perez, F.; Solans, X.; Vazquez, S. *Angew. Chem., Int. Ed*. **1995**, *34*, 912. (e) Fessner, W. D.; Murty, B. A. R. C.; Prinzbach, H. *Angew. Chem., Int. Ed*. **1987**, *26*, 451.

JA070254L