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VIP Photochemical Synthesis

Complexity from Simplicity: Tricyclic Aziridines from the Rearrangement of Pyrroles by Batch and Flow Photochemistry**

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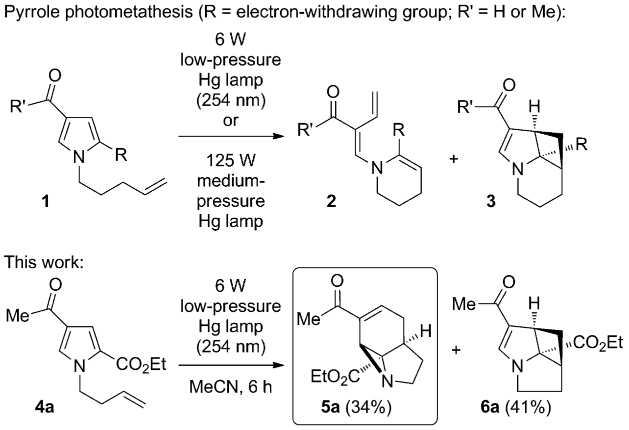
The use of photochemistry has a long and rich history in organic synthesis. Performing reactions specific to an excited state by simple UV irradiation can enable a low cost, environmentally benign, reagent- and catalyst-free entry to molecular complexity. For example, the alkene [2+2] cycloaddition has proven to be a photochemical workhorse in the construction of complex natural products.[1] In the field of arene photochemistry, the *meta*-photocycloaddition reaction is an outstanding example of the extensive bond reorganization that can only be achieved through a photo-induced excited state.[2] The application of this reaction in natural product synthesis has been demonstrated by the pioneering studies of Wender and others.[3] In contrast, the photochemistry of nitrogenous heteroaromatic systems is less advanced, although useful procedures, involving rearrangement[4,5] and reactive-intermediate solvation,[6] have been developed and applied in synthesis. Herein, we report a novel and general photochemical reaction sequence that results in the formation of tricyclic, fused aziridine ring systems from simple pyrrole derivatives.

Previously, we described the intramolecular photometathesis of pyrroles.[7] Specifically, UV irradiation of *N*-pentenylpyrrole derivatives, such as **1**, resulted in the formation of triene **2** by way of a metathetic sequence, involving [2+2] cycloaddition of the alkene tether to the C2–C3 pyrrole bond, followed by retro [2+2] cycloaddition to give **2** (Scheme 1). Studies of a specific example showed that the reaction proceeded through two sequential wavelength-dependent reactions involving [2+2] cycloaddition at less than 280 nm followed by a *retro*-[2+2] cycloaddition of the resulting cyclobutane **3** at wavelengths longer than this. Generally speaking, irradiation with a low-pressure UVC lamp (predominantly 254 nm) gave a mixture of cyclobutane and triene with good overall mass balances. Irradiation with a higher-power medium-pressure (broadband) lamp gave mainly the metathesis product with shorter reaction times.



Scheme 1. Photocycloaddition reactions of pyrroles.

While investigating the scope of this chemistry, we synthesized the *N*-butenylpyrrole **4a**, as the resultant strained tricyclic cyclobutane **6a** was of interest for other studies. Irradiation of **4a** (1 mmol) with a low-pressure source for six hours, followed by concentration of the photolysate and purification resulted in the recovery of **4a** (18%), the expected cyclobutane **6a** (41%), and a third product **5a** (34%), which was clearly not the initially assumed metathesis product (i.e., **2**). After detailed analysis, the structure of **5a** was confirmed to be the 1-azatricyclo[4.2.1.0^{2,9}]non-3-ene ring system,[8] which results from a remarkable and hitherto unreported cycloaddition–rearrangement sequence (Scheme 1). The complexity of this product, and the fact that reducing the length of the pyrrole–alkene tether by just one atom had led to such a different outcome, prompted us to investigate the scope of this fascinating sequence.

A range of *N*-but-3-enylpyrroles, which possess varying degrees of ring substitution, were prepared using a number of common reported methods (see Supporting Information). These pyrroles were then all irradiated at 254 nm using a 6 W low-pressure UVC lamp in a quartz immersion well apparatus. Aziridine formation was observed in all 14 examples (Scheme 2). The only key requirement appeared to be an electron-withdrawing group at C2 of the pyrrole, as substrates without it failed to react or underwent photodecomposition. The reaction was very tolerant toward substituents at all pyrrole carbon atoms, ranging from monosubstituted (e.g., **5k,l**), to tetrasubstituted examples (e.g., **5f**). In view of the strained tricyclic aziridine ring system, it is remarkable that products containing two adjacent quaternary centers (e.g., **5f,i,j**) can be routinely formed in the course of the reaction. In most cases, the mass balance of the reaction, including the

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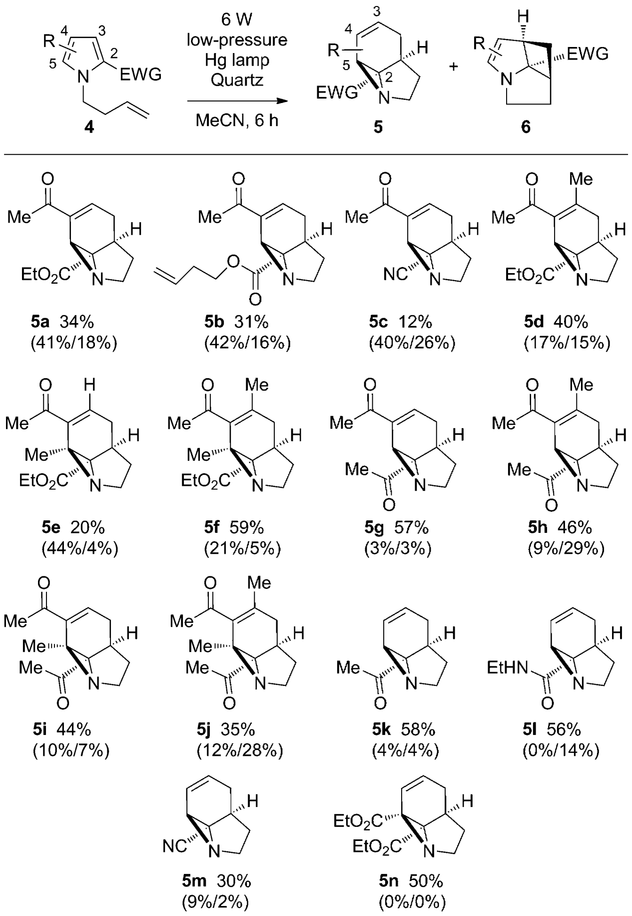


Scheme 2. Photocycloaddition–rearrangement of pyrroles to aziridines. Reaction conditions: **4** (1 mmol) in MeCN (170 mL). For irradiation times, see the Supporting Information. All products are racemic. Results in brackets: yield of **6**/recovered **4**.

cyclobutane and the recovered pyrrole, was generally 70–90%. This result indicated a relatively clean reaction sequence with little loss to side reactions. Some of the less successful examples included cyano substitution at C2. In the case of **4m** (R/R′/R″ = H, EWG = CN), detectable amounts of the photochemically rearranged 3-cyano pyrrole isomer[4c] were obtained during the course of the reaction.

The cyano products **5c** and **6c** proved to be highly crystalline, thus enabling the growth of suitable crystals for X-ray analysis of their molecular structures. Figure 1 shows their highly compact tricyclic shapes.

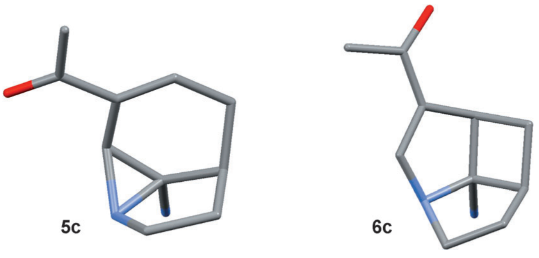
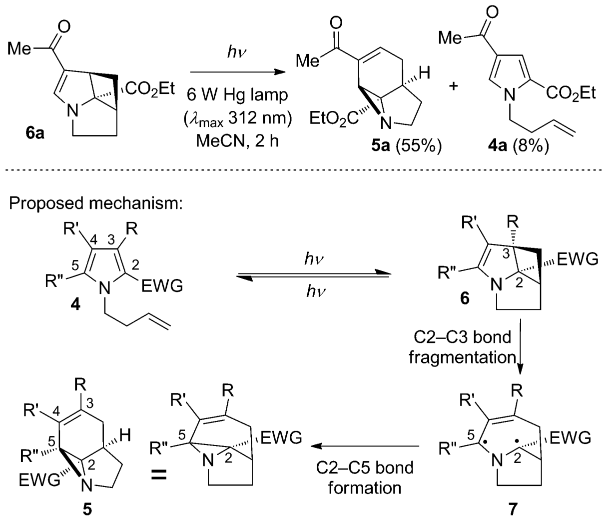


Figure 1. X-ray crystal structures of aziridine **5c** and cyclobutane **6c** (hydrogen atoms omitted for clarity).

Variations in the ratios of isolated products and starting pyrrole suggested a photochemical equilibration sequence that likely involves compounds **6**. A pure sample of **6a** (0.9 mmol) was irradiated with a low-pressure phosphor-coated UVB Hg lamp with the maximum emission centered at 312 nm (Scheme 3). After two hours, **6a** was completely consumed, and aziridine **5a** and pyrrole **4a** were isolated in 55% and 8% yields, respectively. This result clearly indicates that **6a** rearranges mainly to aziridine **5a**, and a small amount of original pyrrole **4a**. It also indicates that the second step is likely more efficient at a longer wavelength.



Scheme 3. Fragmentation studies and proposed mechanism of aziridine formation.

This information led us to propose a plausible mechanistic rationale for the overall reaction. Excitation of the generic pyrrole **4** substituted by an EWG at C2 with a 254 nm low-pressure Hg lamp results in the initial [2+2] cycloaddition across the C2–C3 bond to give cyclobutane **6**. With the lamp used for the experiments shown in Scheme 2, most of the emission is centered at 254 nm with small amounts of radiation at 312 nm. In cyclobutanes that bear an acyl group at C4 (**6a–j**), further excitation leads to the biradical **7** by way of a C2–C3 bond cleavage[9] (by UVB or UVC). This biradical then undergoes C2–C5 bond formation that leads to the aziridine ring in the final product **5**. UV spectroscopy of the cyclobutane **6a** displays a λ_{max} at around 300 nm, consistent with the vinylogous amide chromophore present in all the examples **6a–j**. Although this feature is well matched by the 312 nm emission from the fluorescent UVB Hg lamp in Scheme 3, this output would be minimal from the uncoated UVC lamp used in Scheme 2. However, for these cyclobutane reaction intermediates, the extinction coefficient at 254 nm is strong enough ($\varepsilon \geq 1500\ \mathrm{mol^{-1}\,m^{3}\,cm^{-1}}$) to ensure efficient excitation with the UVC lamp used in Scheme 2. In examples where there is no substitution on the C4 atom of pyrrole (**4k,l,m**), the situation is more clear-cut. For example, irradiation of **4l** (EWG = CONHEt, R/R′/R″ = H) with the short-wavelength lamp gave isolated aziridine **5l** in 56%

yield, but no isolated cyclobutane. Similarly, the related pyrroles **4k** and **4m** were transformed to mainly aziridine product. Significantly, the cyclobutane **6l** (EWG = CONHEt, R/R′/R″ = H), isolated from an incomplete irradiation of **4l**, did not react when it was subjected to irradiation with the UVB lamp at 312 nm (see Scheme 3). The UV spectrum of **6l** shows no features above λ_{max} centered at 230 nm. Therefore it is likely that in these types of pyrroles, both steps of the sequence are excited by the 254 nm emission.

Clearly these results present a fascinating divergence in reactivity compared to the *N*-pentenyl-bearing examples previously studied (i.e., **1** to **2**). Why such different outcomes are observed when essentially identical cyclobutane intermediates (i.e., **3** and **6**) appear to be involved remains unexplained at this stage. Further theoretical and experimental studies are currently being undertaken to understand the factors that control aziridine formation versus metathesis from cyclobutane intermediates, as well as the regioselectivity of the cycloaddition of **4** to **6**.

Finally we investigated the scale-up potential of these reactions. Although synthetic photochemistry is capable of producing highly complex molecules from simple starting materials, it is often criticized for being limited to small-scale use. In 2005, we reported a simple and general flow reactor for the scale-up of organic photochemistry.[10] The original reactor was constructed of layers of tightly coiled UV-transparent fluorinated ethylene propylene (FEP) wrapped around a water-cooled Pyrex or Vycor glassware vessel, into which a high-power medium-pressure mercury lamp was placed. The reaction solution could then be flowed around the lamp by means of an HPLC or peristaltic pump. For reactions that possess moderate to high quantum yields, our group and others[11] have found that this simple device is capable of producing more than 100 g of products per day in a single pass.

We were interested in developing a similar FEP reactor that could process these pyrroles using low-pressure UVB and UVC sources,[12] as the use of high-power medium-pressure lamps caused degradation in this reaction. Since the 6 W low-pressure lamp was only capable of producing a maximum of 0.5 W of usable UV, we constructed an FEP reactor based on the dimensions of a 36 W PL-L lamp ($\lambda_{max} = 254$ nm) with much higher power (see Figure 2). A single layer of FEP tubing was wrapped tightly around a quartz tube, into which a single 36 W PL-L lamp was inserted (see the Supporting Information for construction details). The pyrrole solution was then flowed through the reactor by means of a valveless piston pump. Two electronically different pyrroles were chosen to test the efficacy of this reactor, and the optimized results are shown in Scheme 4.

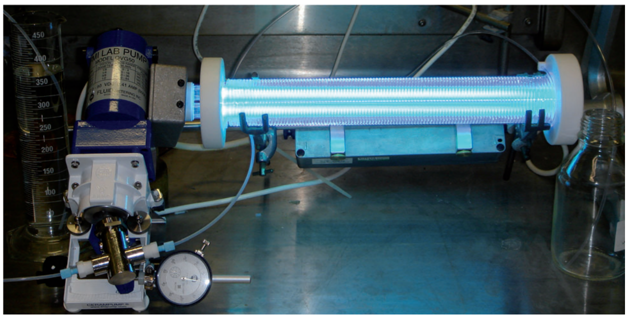
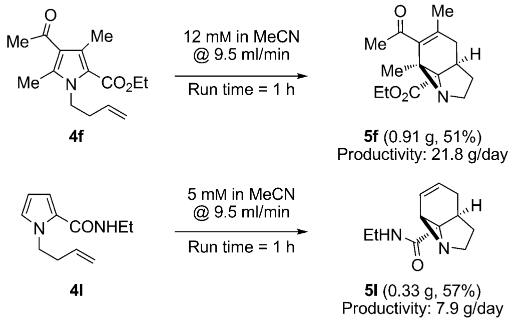


Figure 2. FEP flow reactor with a 36 W 254 nm PL-L lamp.



Scheme 4. Continuous photorearrangement of pyrroles in the FEP flow reactor shown in Figure 2.

In an optimized[13] one hour run, processing of **4f** (9.5 mL min^{-1}; 12 mM) gave 0.91 g (51 % yield, 21.8 g day^{-1}) of isolated **5f**. Similarly, the mono-substituted **4l** was processed for one hour (9.6 mL min^{-1}; 5 mM) to give 0.33 g (57 %, 7.9 g day^{-1}) of isolated **5l**. It is noteworthy that both these reactions could be processed continuously with similar isolated yields observed for the batch reactions (see Scheme 2). A compact modular array of just five of these reactors should enable the synthesis of more than 100 g per day of **5f** in a single fumehood.[14] These results highlight the impressive level of productivity of flow photochemistry. It would likely be much more difficult to achieve this productivity through batch reactions, because the dimensions of the 36 W PL-L lamp would require a custom made large-area/small-volume immersion well that would require constant drainage and refilling.

In summary, a novel photochemical sequence for the conversion of substituted pyrroles into complex tricyclic, fused aziridines has been discovered and has proved general for mono- to tetrasubstituted examples. The reaction has been shown to proceed through an initial [2+2] cycloaddition followed by rearrangement, which we propose proceeds through a fragmentation–recombination pathway via a biradical. By using a single FEP flow reactor, we have shown that multigram quantities of products can be produced continuously. This combination of easily accessible molecular complexity and scalability will likely make these tricyclic aziridine products the focus of further synthetic studies.

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[13] Optimized by variation of both flow rate and concentration. For example, in one hour runs, an 11.7 mM solution of **41** @9.5 mL$\,$min^{-1} and @4.8 mL$\,$min^{-1} gave **51** in 20 and 50% yield, respectively.

[14] This device is currently under construction and will enable the simultaneous use of both UVC (254 nm) and UVB (312 nm) lamps. This will hopefully maximize the yield of aziridine by equilibrating (Scheme 3) any pyrrole/cyclobutane products formed during their residence in the flow reactor.