This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
A Photochemical Ring Expansion of 6- to 8-Membered Nitrogen Heterocycles by [1,3]-Sigmatropic Rearrangement.**

Morgan A. Manning, Wei Sun, Mark E. Light, and David C. Harrowven.

Abstract: A new route to azocines and benzoazocines from furopyridinones is described through a photochemically induced [1,3]-sigmatropic rearrangement. The method gives access to these 8-membered nitrogen heterocycles from dimethyl squarate in four stages and with excellent atom economy by sequencing thermal and photochemical ring expansion steps under continuous flow.

Azocanes and their unsaturated analogues form a class of 8-membered nitrogen heterocycles that includes the manzamine alkaloids and other natural products. Though they have the attributes of a privileged structure in medicinal chemistry, they remain underexploited in that context due to challenges associated with their synthesis. In particular, syntheses based on 'end-to-end' cyclisation strategies have to overcome transannular strain and the loss of entropy on ring closure, making it necessary to employ high dilution or pseudo-high dilution conditions to reduce competing intermolecular reactions. Herein we describe a new route to azocines and benzoazocines by photo-induced ring expansion of vinyl- and aryl-furopyridinones respectively (Scheme 1).

The discovered was made during a follow-up study on the thermal rearrangement of aminocyclobutenones to furopyridinones. The presence of an extended chromophore in the products prompted us to examine their photochemistry. Pleasingly, when an acetonitrile solution of 2a was irradiated with UVA light (λ = 370 nm, 36W) under continuous flow, using a set-up akin to that described by Booker-Milburn and Berry et al., it gave furoazocine 3a in 48% yield (Scheme 2). Similarly, furopyridinones 2b and 2c gave furoazocines 3b and 3c in 47% and 54% yield respectively on irradiation.

Attention next turned to aryl-substituted furopyridinones, which were readily prepared by thermal rearrangement of the corresponding alkynylcyclobutenones 4 (Scheme 4 & Supporting Information). Each underwent ring expansion on irradiation with UVA to give the corresponding benzoazocines 6a-h (Tables 1-2) with a skipped diene unit. Yields were typically in the range of 51-74%, except for substrate 5h with the electron deficient arene which was significantly lower (28%). Cases where the migrating bond was between two benzylic centres, e.g. 6i-n (Table 2), were also high yielding and notably gave benzoazocines as single diastereomers. Their
relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).

The mechanistic course of the reaction was next examined by TD-DFT,\(^{18}\) using 5a \(\rightarrow\) 6a as the exemplar. Calculations showed that the singlet excited state \(^1\)[5a]* could relax directly to azocine 7a via a 1,3-sigmatropic rearrangement (Figure 2),\(^{19}\) before giving benzoazocine 6a via a thermal [1,5]-sigmatropic H-shift (estimated \(E_a = 16.0\) kcal/mol).\(^{20}\)

Interestingly, for the related thiophene derivative 5n the conjugated tetraene 7n was evidenced as an intermediate by \(^1\)H NMR, albeit as a mixture with 6n. On standing that sample underwent isomerization to give tris-heterocycle 6n as the sole product (Scheme 3). TD-DFT analysis indicated that the barrier for the [1,5]-H-shift, 7n \(\rightarrow\) 6n (26.7 kcal/mol, see Supporting Information), was significantly higher than for 7a \(\rightarrow\) 6a, suggesting that isomerization may be by protonation and deprotonation in this case. The method was then extended to the 2-thiophenyl and 3-pyridyl analogues, 5o and 5p with both giving a tris-heterocyclic product, 6o and 6p, albeit in low yield with the electron deficient heteroaromatic (Scheme 4).

Table 1. Benzoazocines from furopyridinones following UVA irradiation.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mass Spectra</th>
<th>Relative Stereochemistry</th>
<th>X-Ray Crystallographic Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a, 61%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6b, 70%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6c, 51%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6d, 52%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6e, 57%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6f, 58%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6g, 70%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
<tr>
<td>6h, 28%</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
</tbody>
</table>

Table 2. Photochemical rearrangements of diarylfuropyridinones.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mass Spectra</th>
<th>Relative Stereochemistry</th>
<th>X-Ray Crystallographic Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6i-m</td>
<td>(\text{MeCN, 2 h,}^{17})</td>
<td>(\text{continuous flow})</td>
<td>(\text{Relative stereochemistry was confirmed by x-ray crystallographic analysis of 6i and 6l (Figure 1).})</td>
</tr>
</tbody>
</table>

Figure 1. X-ray crystal structures of benzoazocines 6i [CCDC 1969077] and 6l [CCDC 2025763].

Figure 2. Calculated free energy barriers for the rearrangement of 5a.
Finally, we have been able to produce benzoazocines 6 from alkylnyclobutenones 4, directly and in high yield, by sequencing the respective thermal and photochemical rearrangements under flow (Scheme 5). Thus, dioxane solutions of cyclobutenones 4a,e,g,i,l were first subjected to thermolysis at 210 °C for a residence time of 100 min, then irradiated with UVA light from 6 × 1.7 W LEDs for 10 min to give the corresponding benzoazocines 6a,e,g,i,l in 74-84% yield. Notably, the efficiency with which each starting material was prepared ensured that these four-stage sequences from dimethyl squarate 8 each proceeded in ~50% overall yield.21

 Sequential thermal and photochemical rearrangements were also effective with alkylnyclobutenone 1c (Scheme 6). In this case it was found advantageous to conduct the thermolysis in two stages due to its poor conversion to the intermediate furyropyridine 2c following a single pass at 160 °C. As with the aforementioned examples, the overall yield of azocine 3c given after sequencing these steps under continuous flow was substantially higher than that achieved using stepwise procedures.21

In conclusion, we have developed a new route to azocines and benzoazocines involving the photochemical ring expansion of furyropyridines. The ease with which these products can be prepared from dimethyl squarate 8 in high yield and diastereoselectivity, and with excellent atom economy, makes this an attractive entry to a class of nitrogen heterocycles that is difficult to access using classical procedures.

Author contributions: Dr. Wei Sun and Morgan Manning contributed equally in respect of the experimental work, with Dr. Mark Light performing the X-ray analyses and Prof. David Harrowen supervising the work. We gratefully acknowledge financial support from the European Regional Development Fund [ERDF Interreg Va programme (Project 121)] and EPSRC [EP/P013341/1, EP/L003325/1 and EP/K039466/1]. There are no conflicts of interest to declare.

Notes and references


Scheme 4. Further examples involving heteroatomic ring systems.17

Scheme 5. Preparation of cyclobutenones 4 and conversion to benzoazocines 6 by sequenced thermal and photochemical rearrangement under continuous flow.

Scheme 6. Sequenced thermal and photochemical rearrangement of cyclobutenone 1c to azocine 3c under continuous flow.
A significant loss of mass balance to mixed fractions occurs with an unknown impurity accounting for ca. 5% of its mass. The photochemical experiments described in Tables 1 and 2 were conducted using a 36W Philips UVA lamp [PL36/10/4P] that delivered ~10 W UVA irradiation for a reactor volume of 120 mL [UVA irradiation density ~0.08 W/mL]. In Schemes 2-6, a bespoke UVA LED reactor was used that delivered ~12 W UVA irradiation for a reactor volume of 10 mL. The irradiation density in this case was substantially higher at ~1.2 W/mL. See Supporting information for details.
