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COMMUNICATION

A Photochemical Ring Expansion of 6- to 8-Membered Nitrogen Heterocycles by [1,3]-Sigmatropic Rearrangement.**

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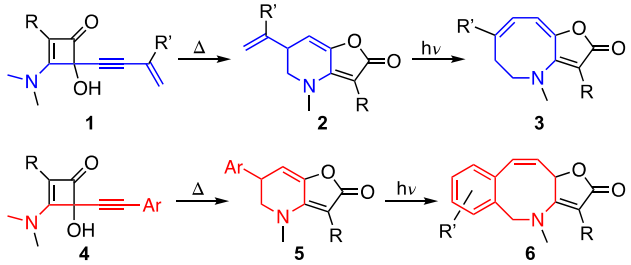
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

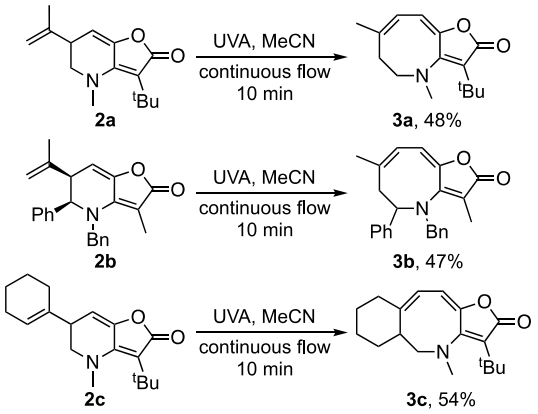
Abstract: A new route to azocines and benzoazocines from furopyridinones is described through a photochemically induced [1,3]-sigmatropic rearrangement. The method gives access to these 8-membered nitrogen heterocycles from dimethyl squarate in four stages and with excellent atom economy by sequencing 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.[1-5] Though they have the attributes of a privileged structure in medicinal chemistry,[6] they remain underexploited in that context due to challenges associated with their synthesis.[7] In particular, syntheses based on 'end-to-end' cyclisation strategies have to overcome transannular strain and the loss of entropy on ring closure,[3,7,8] making it necessary to employ high dilution or pseudo-high dilution conditions to reduce competing intermolecular reactions.[9] Herein we describe a new route to azocines **3** and benzoazocines **6** by photo-induced ring expansion of vinyl- and aryl-furopyridinones **2** and **5** respectively (Scheme 1).[10,11] In addition we show how the same products can be formed directly from alkynylcyclobutenones **1** and **4** by sequencing thermal and photochemical rearrangements under flow.[11,12]



Scheme 1. Sequential thermal and photochemical ring expansion reactions for the synthesis of azocines and benzoazocines from cyclobutenones.

The discovered was made during a follow-up study on the thermal rearrangement of aminocyclobutenones **1/4** to furopyridinones **2/5**.[10,12] The presence of an extended chromophore in the products prompted us to examine their photochemistry.[13] 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.*,[13-15] 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.



Scheme 2. Photochemical ring expansions of furopyridinones to azocines.[16,17]

Attention next turned to aryl-substituted furopyridinones **5a–h**, which were readily prepared by thermal rearrangement of the corresponding alkynylcyclobutenones **4** (Scheme 4 & Supporting Information).[10] 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.* **5i-n** (Table 2), were also high yielding and notably gave benzoazocines **6i-n** as single diastereoisomers. Their

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** Dedicated to Prof. Kevin Booker-Milburn on the occasion of his retirement. Electronic Supplementary Information (ESI) available: Experimental accounts, spectral and analytical details together with copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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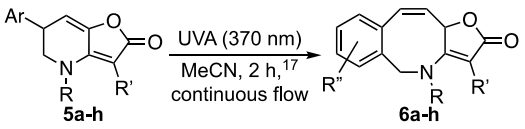
Table 1. Benzoazocines from furopyridinones following UVA irradiation.



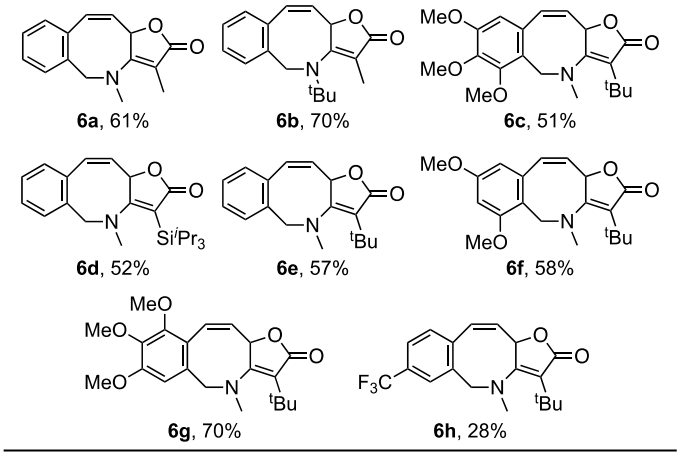
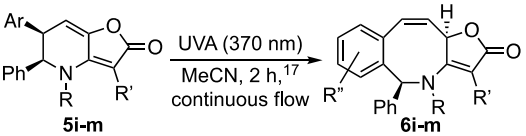
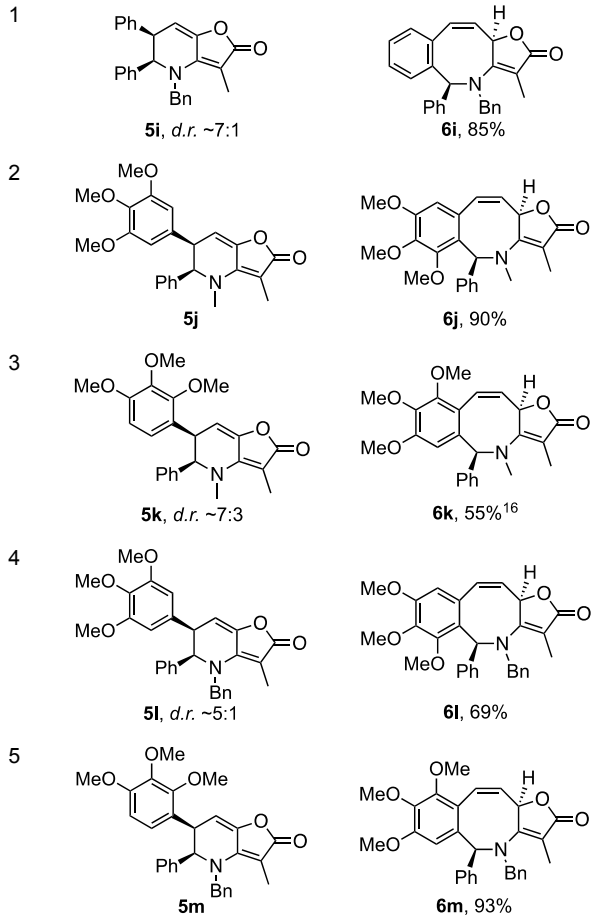


Table 2. Photochemical rearrangements of diarylfuropyridinones.





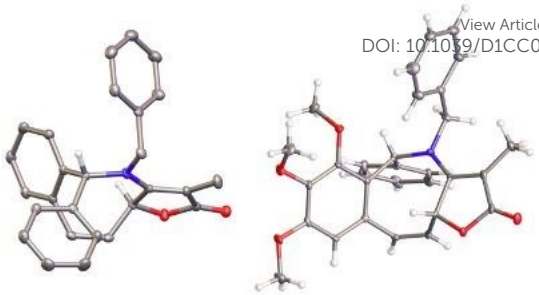


Figure 1. X-ray crystal structures of benzoazocines **6i** [CCDC 1969077] and **6l** [CCDC 2025763]

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** → **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]

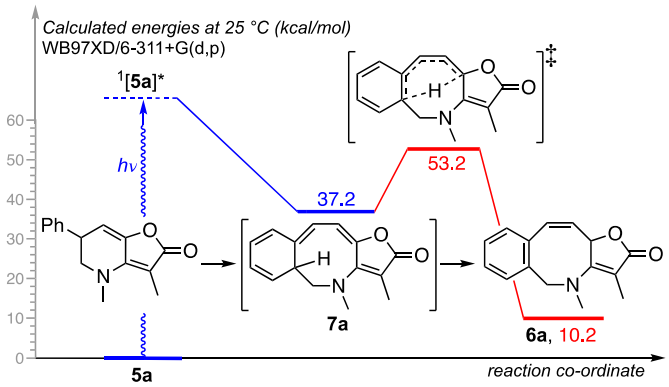
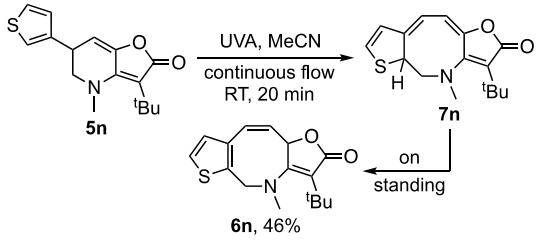
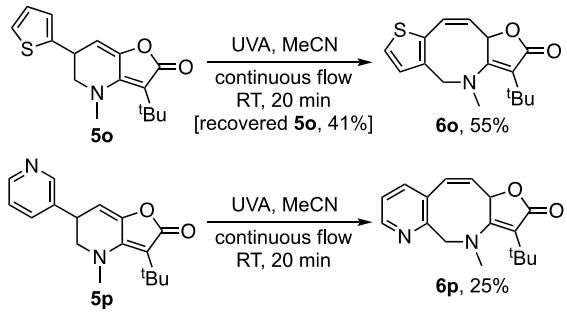


Figure 2. Calculated free energy barriers for the rearrangement of **5a**.

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** → **6n** (26.7 kcal/mol, see Supporting Information), was significantly higher than for **7a** → **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).

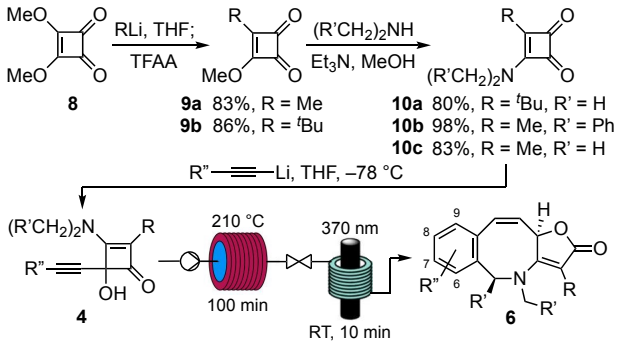


Scheme 3. Evidence for the intermediacy of polyene **7** was provided by extension to the heteroaromatic analogue **5n**.[17]



Scheme 4. Further examples involving heteroaromatic ring systems.[17]

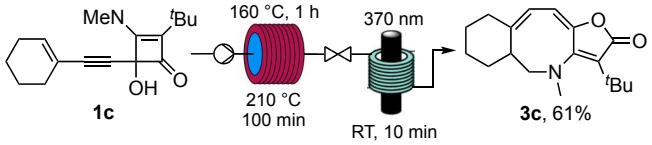
Finally, we have been able to produce benzoazocines **6** from alkynylcyclobutenones **4**, directly and in high yield, by sequencing the respective thermal and photochemical rearrangements under flow (Scheme 5). Thus, dioxane solutions of cyclobutenones **4a**,**e**,**g**,**i**,**l** were first subjected to thermolysis at 210 °C for a residence time of 100 min, then irradiated with UVA light from 6 x 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]



		R	R'	R"			R	R'	R"
4a	lit.	Me	H	Ph	**6a**	74%	Me	H	H
4e	96%	^{t}Bu	H	Ph	**6e**	81%	^{t}Bu	H	H
4g	89%	^{t}Bu	H	3,4,5-(MeO)$_3$Ph	**6g**	81%	^{t}Bu	H	7,8,9-triOMe
4i	95%	Me	Ph	Ph	**6i**	84%	Me	Ph	H
4l	67%	Me	Ph	2,3,4-(MeO)$_3$Ph	**6l**	77%	Me	Ph	6,7,8-triOMe

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

Sequential thermal and photochemical rearrangements were also effective with alkynylcyclobutenone **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 furopyridinone **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 achieve using stepwise procedures.[21]



Scheme 6. Sequenced thermal and photochemical rearrangement of cyclobutenone **1c** to azocine **3c** under continuous flow.

In conclusion, we have developed a new route to azocines and benzoazocines involving the photochemical ring expansion of furopyridinones. 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.

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DOI: 10.1039/D1CC00703C

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 Harrowven 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.

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16 Examples of the rearrangements **2** → **3** were limited by the availability of enynes from commercial suppliers, and on-going COVID restrictions. Compound **6k** was contaminated with an unknown impurity accounting for *ca.* 5% of its mass.

17 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.

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21 A significant loss of mass balance to mixed fractions occurs on purification of furopyridinones **2** and **5** by column chromatography. We believe this to be the primary reason for the yield elevation observed when the thermal and photochemical steps are sequenced.