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Cascade reactions of 1,2,4-triazines: direct thermochemical access to functionalized 4,5-dihydroazocines

Steven A. Raw* and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

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Abstract—A rapid, facile approach to functionalized 4,5-dihydroazocines has been developed, exploiting a one-pot reaction cascade from easily-prepared 3-(ethoxycarbonyl)-5-phenyl-1,2,4-triazine, cyclobutanone and secondary amines.

4,5-Dihydroazocines are of interest to the organic chemist as eight-membered nitrogen-containing rings are found in many bioactive agents and naturally occurring compounds.[1] For example, in the site specific cocaine abuse treatment agent **1**,[1c] the anti-insectan natural product supinine C **2**[1e] and the substituted dihydroazocine **3**,[1f] which displays anti-exploratory behaviour in mice (Fig. 1).

As part of our ongoing interest in the synthesis and utilization of nitrogen-containing heterocyclic and heteroaromatic compounds,[2] we recently had cause to explore Boger's procedure for the conversion of 1,2,4-triazines **4** into highly substituted pyridines **6**.[3] This chemistry exploits the inverse-electron demand Diels–Alder reaction of triazines and enamines. With highly substituted triazines, however, we obtained only the dihydropyridines **5**, which could then be aromatized via a Cope elimination (Scheme 1).[4]

The electrocyclic ring expansion of transient, strained dihydropyridines **5**, formed by the photochemical [2 + 2]-cycloaddition of acrylonitriles to pyridines, to give dihydroazocines has recently been reported.[5] These

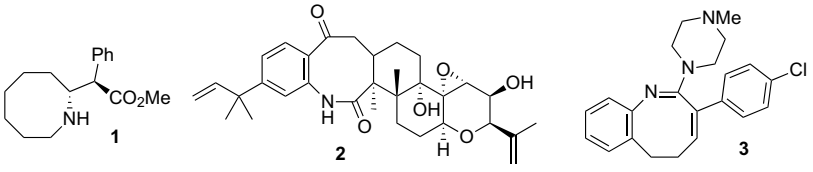
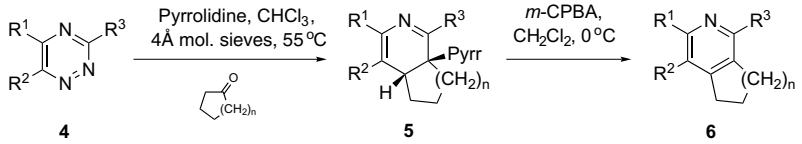


Figure 1. Bioactive compounds possessing eight-membered nitrogen-containing rings.



Scheme 1. From 1,2,4-triazines to polysubstituted pyridines.

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* Corresponding authors. Tel.: +44 0 1904 432 606; fax: +44 0 1904 434 523; e-mail addresses: steven.raw@astrazeneca.com; rjkt1@york.ac.uk

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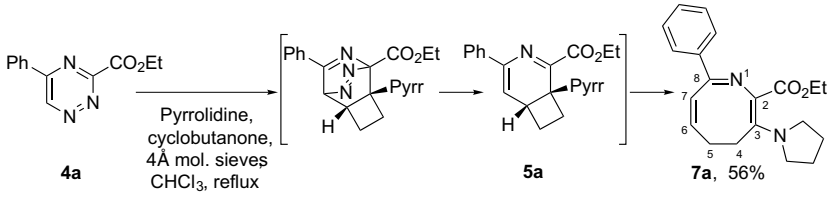
reactions can, however, suffer from a lack of regioselectivity.[5b,c] The formation of 4*H*-azepines from transient dihydropyridines produced by the reaction of 1,2,4-triazines with cyclopropenes is also known.[6]

In the light of these insights, and in view of the interest in dihydroazocines, we reasoned that an enamine derived from cyclobutanone and a secondary amine would react with 1,2,4-triazines **4** to form a transient, strained dihydropyridine **5a** with good regioselectivity. The mode of addition of enamines to 3-substituted 1,2,4-triazines is known to be highly selective.[3c] This strained dihydropyridine **5a** should then undergo electrocyclic ring expansion to furnish the 4,5-dihydroazocine **7** in a four-step reaction cascade. In pursuit of this objective, triazine **4a** was heated with cyclobutanone, pyrrolidine and 4 Å molecular sieves in $CHCl_3$ at reflux. Gratifyingly, after complete consumption of **4a**, the desired 4,5-dihydroazocine **7a** was isolated in a yield of 56% (Scheme 2).[7,8]

The NMR spectroscopic data for **7a** were consistent with those expected and the structure was confirmed by comparison of these data to those reported for analogous compounds.[5a,b] The *cis* stereochemistry of the C-6/C-7 alkene (and hence that of the C-2/C-3 double bond) expected from a disrotatory [4+2]-electrocyclic reaction of systems such as **5a** was confirmed by the observation of an H–H coupling constant of ~12 Hz, within the range indicative of *cis* alkenes. Furthermore, ^{1}H NMR spectroscopy of the crude reaction mixture showed none of the other regioisomer.

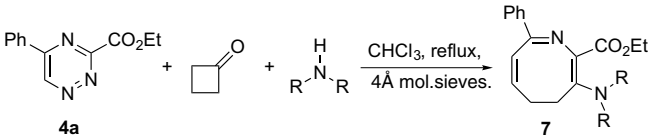
With this result in hand, we went on to investigate the scope of this reaction with respect to the amine portion and the results are summarized in Table 1.

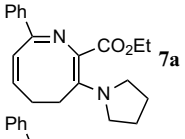
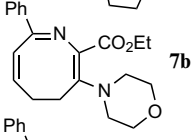
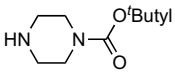
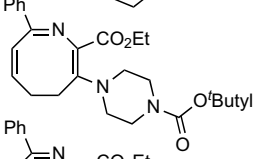
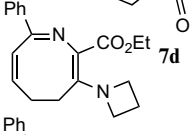
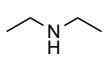
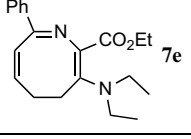
As can be seen, a variety of cyclic amines can be utilized under these conditions (entries i–iv), giving the 4,5-dihydroazocines **7a–d** in fair to good yields. Acyclic amines, exemplified by diethylamine (entry v), have also



Scheme 2. Functionalized 4,5-dihydroazocines from 1,2,4-triazines.

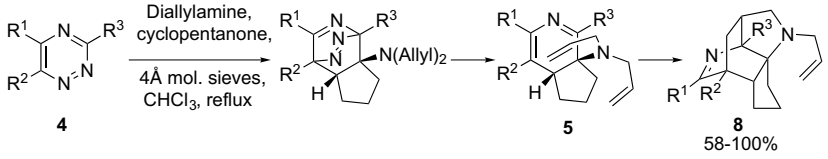
Table 1. Conversion of 1,2,4-triazine **4a** into 4,5-dihydroazocines **7**.[7,8]



Entry	Amine	4,5-Dihydroazocine	Time (h)	Isolated yield (%)
i		 **7a**	2.5	56
ii		 **7b**	7 (then 15 h at rt)	71
iii		 **7c**	7 (then 15 h at rt)	52
iv		 **7d**	22	26
v		 **7e**	22	73

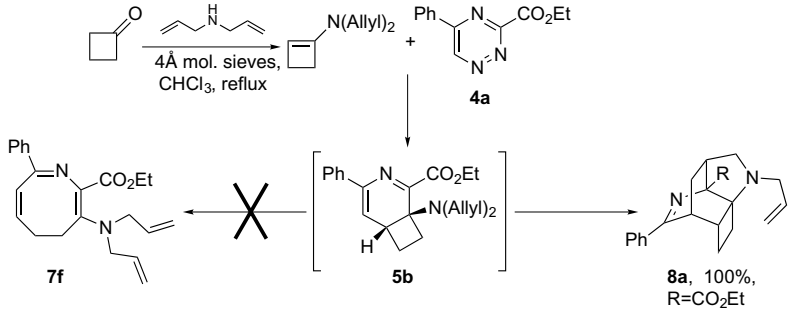
been shown to be good partners in this reaction. To the best of our knowledge, this cascade represents the first use of the reaction between enamines and 1,2,4-triazines as a thermochemical approach to 4,5-dihydroazocines **7**.[9]

We have recently described the direct conversion of 1,2,4-triazines **4** into complex nitrogen-containing polycyclic compounds **8** (Scheme 3).[10] In this multi-step process, carbonyl compounds and secondary allyl amines are reacted in the presence of a 1,2,4-triazine **4** to give the corresponding enamines. These undergo a Diels–Alder retro-Diels–Alder process to form the dihydropyridines **5**, which then undergo a spontaneous intramolecular Diels–Alder reaction of the vinyl unit to form the polycycle **8**.



Scheme 3. Conversion of 1,2,4-triazines **4** into nitrogen-containing polycyclic compounds **8**.

As both the dihydroazocine-producing cascade discussed in this communication and the polycycle-producing cascade[10] exploit a dihydropyridine intermediate **5**, we were interested in studying the competition between [4+2]-cycloaddition and electrocyclic ring expansion. To this end, the reaction of **4a** and cyclobutanone was repeated with diallylamine as the amine (Scheme 4). The intermediate dihydropyridine formed **5b** could then, in principal, undergo either type of pericyclic reaction.



Scheme 4. [4+2]-Cycloaddition versus electrocyclic ring expansion.

As shown, 7-allyl-11-phenyl-9-(ethoxycarbonyl)-7,10-diazatetracyclo[6.3.1.0.^{2,6}0^{6,9}]dodec-10-ene **8a** was isolated in quantitative yield. This implies that, in this case at least, the [4+2]-cycloaddition of an internal dienophile is significantly faster than electrocyclic ring expansion.

In conclusion, we have established a cascade reaction sequence from 1,2,4-triazine **4a** which, in a single, operationally simple manipulation, allows formation of 4,5-dihydroazocines **7**. This one-pot cascade sequence comprises enamine-formation, inverse-electron-demand Diels–Alder reaction, retro-Diels–Alder reaction and electrocyclic ring opening. We are currently optimizing this process, broadening the scope of the chemistry and applying it to target syntheses. Furthermore, we intend to assess the 4,5-dihydroazocines produced in this work for bioactivity as part of an existing collaboration.

Acknowledgements

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Reference and notes

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4. As a consequence, we developed a tethered imine–enamine methodology (TIE) for the direct conversion of 1,2,4-triazines into pyridines, which avoids the need for a second, discrete aromatization step: Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2004**, 508.
5. (a) Sakamoto, M.; Sano, T.; Fujita, S.; Ando, M.; Yamaguchi, K.; Mino, T.; Fujita, T. *J. Org. Chem.* **2003**, *68*, 1447; (b) Donati, D.; Fusi, S.; Ponticelli, F. *Eur. J. Org. Chem.* **2002**, 4211; (c) Donati, D.; Fusi, S.; Ponticelli, F. *Tetrahedron Lett.* **1996**, *37*, 5783.
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7. All novel compounds were fully characterized by NMR spectroscopy and HRMS.
8. Representative procedure: Ethyl 8-phenyl-3-pyrrolidin-1-yl-4,5-dihydroazocin-2-carboxylate **7a**. To a solution of ethyl 5-phenyl-[1,2,4]triazine-3-carboxylate **4a** (0.10 mmol, 0.023 g) in $CHCl_3$ (1 mL) was added sequentially powdered 4 Å molecular sieves (0.10 g), cyclobutanone (0.30 mmol, 0.022 mL) and pyrrolidine (0.30 mmol, 0.025 mL). The mixture was heated to reflux for 2.5 h, then cooled to rt, filtered through a cotton wool plug and concentrated in vacuo. Purification by flash chromatography on neutral alumina (Brockmann grade 1, deactivated with 6% w/w H_2O), eluting with CH_2Cl_2 to 9:1 CH_2Cl_2/EtOAc gave the title compound (0.018 g, 56%) as a yellow oil: R_f 0.14 (9:1 CH_2Cl_2/EtOAc); δ_H 1.35 (3H, t, *J* 7.1 Hz), 1.92 (4H, br s), 2.45 (2H, br s), 2.64 (2H, br s), 3.45 (4H, br s), 4.23 (2H, t, *J* 7.1 Hz), 6.03 (1H, dt, *J* 12.6 Hz, ^4J 1.9 Hz), 6.20 (1H, dt, *J* 12.6 Hz, *J* 4.1 Hz), 7.31–7.41 (3H, m), 7.84–7.93 (2H, m); δ_C 14.8 (CH_3), 25.5 (CH_2), 26.8 (CH_2), 27.9 (CH_2), 51.3 (CH_2), 59.8 (CH_2), 115.1 (C), 125.9 (CH), 127.8 (CH), 128.2 (CH), 129.2 (CH), 136.2 (CH), 140.6 (C), 152.5 (C), 158.4 (C), 164.0 (C); *m/z* (CI) 325 (MH^+) [HRMS (CI) calcd for $C_{20}H_{25}N_2O_2$ 325.1916. Found 325.1914 (0.6 ppm error)].
9. Whilst preparing this manuscript, an isolated example of the thermochemical formation of dihydroazocines from 1,2,4-triazines has come to our attention: Elix, J. A.; Wilson, W. S.; Warrener, R. N.; Calder, I. C. *Aust. J. Chem.* **1972**, *25*, 865, In this approach, a strained cyclobutene (dimethyl tricyclo[4.2.2.0^{1,2}]deca-3,9-diene-7,8-carboxylate) is used as the dienophile which, on reaction with ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate in toluene at reflux over seven days, gives the dihydroazocine (23%), accompanied by a double-addition product (26%), see below.

   As well as the obvious drawbacks (extended reaction time, the use of an unusual dienophile and the formation of a double addition product), this approach offers no prospect of regioselectivity if applied to unsymmetrical cyclobutenes.
10. Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260.