Access to 1,2,4-triazines by the telescoped reaction of aziridines and *N*-tosylhydrazones

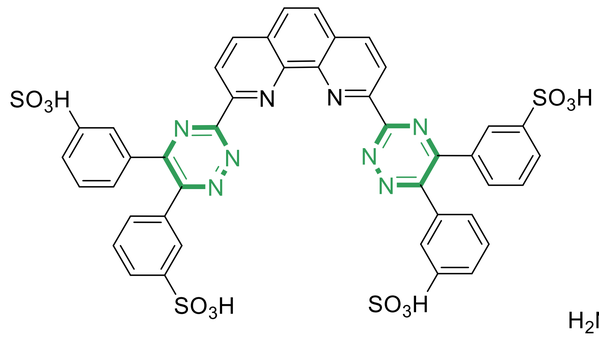
Lorène Crespin,[1] Lorenzo Biancalana,[1] Tobias Morack,[1] David C. Blakemore[2] and Steven V. Ley[1]

[1] Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK
[2] Medicine Design, Pfizer Inc., Eastern Point Road, Groton, Connecticut, 06340, USA
Email : lc667@cam.ac.uk

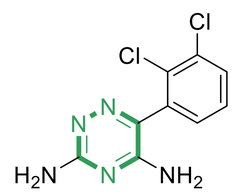
Introduction

1,2,4-Triazine derivatives represent an important class of nitrogen heterocycles, with a wide range of applications:

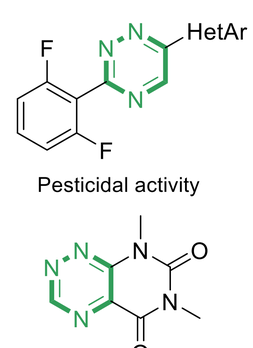
- *Key synthetic building blocks* for the preparation of heterocyclic systems via hetero Diels-Alder cycloadditions [1]
- Can be regarded as *aza-pyrimidines* and used for the synthesis of aza-nucleotides and nucleosides
- *Ligands* for transition metal complexes [2]
- Broad *bioactivities* (medicine and agrochemistry): inflammatory, antitumor, antibacterial, anticonvulsant, antiviral and pesticidal properties [3]



Separating reagent of actinides from lanthanides



Lamictal
Anti-epileptic (GSK)



Pesticidal activity

Fervenulin
Antibiotic

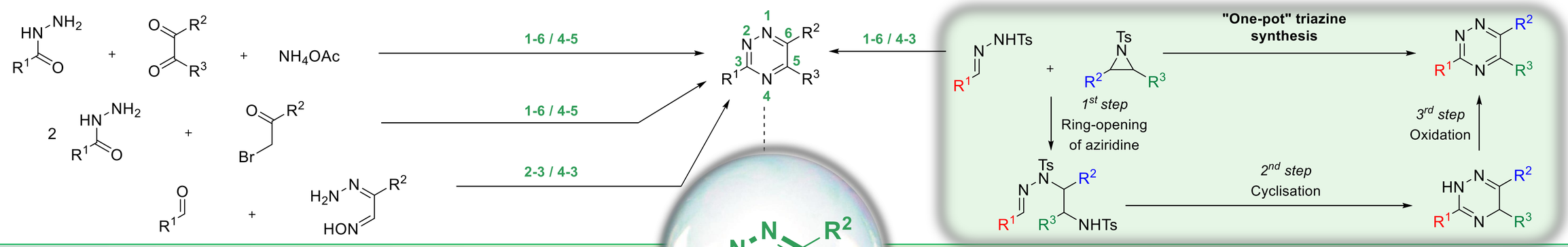
Approaches for 1,2,4-triazines preparation

Previous methods:

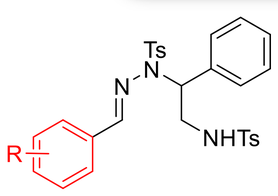
- Many of the reported methods use a 1-6/4-5 disconnection [4]
- Major drawbacks : tedious substrate preparation, harsh reaction conditions and *low regioselectivity* for the synthesis of 3,5,6-trisubstituted triazines [5]

This work: [6]

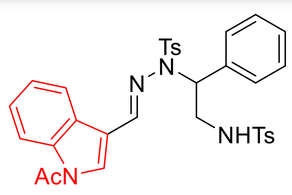
- Conceptually new pathway: *disconnection 1-6/4-3*
- Access to di- and tri-substituted triazines with *only one regioisomer*
- Possibility to isolate aminohydrazones or *telescoped 3-step procedure*



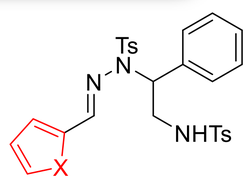
Preparation of aminohydrazones



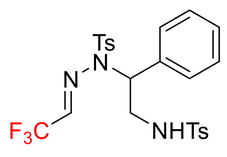
R = H, 91%
R = *p*-Br, 95%
R = *p*-Cl, 94%
R = *p*-F, 92%
R = *p*-CF_3, 92%
R = *p*-OMe, 97%
R = *p*-NO_2, 90%
R = *m*-COOMe, 93%
R = *m*-BPin, 95%
R = *o*-CF_3, 70%



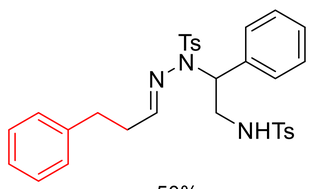
93%



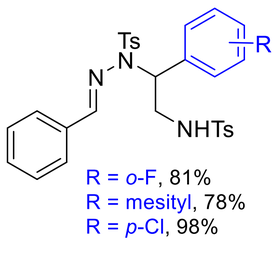
X = O, 84%
X = S, 79%



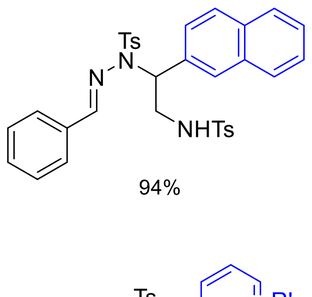
55%



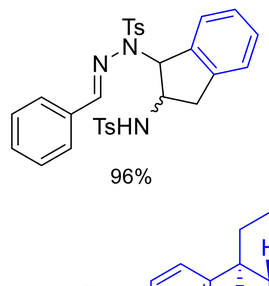
50%



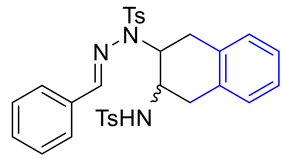
R = *o*-F, 81%
R = mesityl, 78%
R = *p*-Cl, 98%



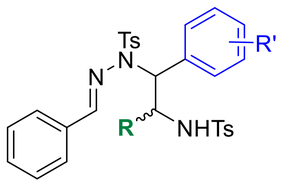
94%



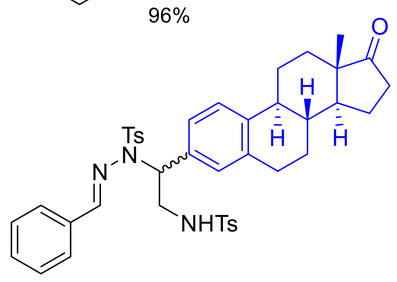
96%



99%

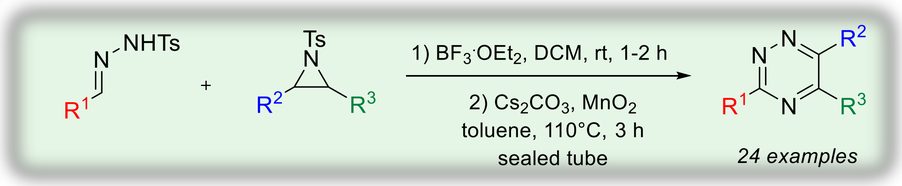


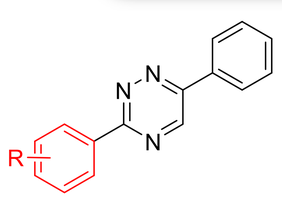
R = Me, R' = H, 95%
R = *i*Pr, R' = Cl, 97%



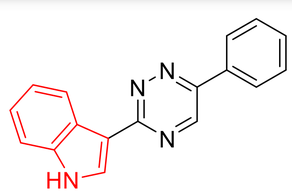
84%

« One-pot » 1,2,4-triazine synthesis

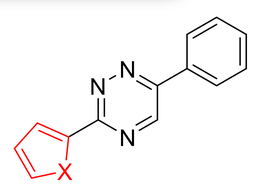




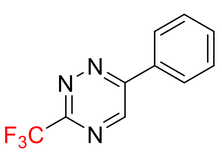
R = H, 41%
R = *p*-Br, 51%
R = *p*-Cl, 56%
R = *p*-F, 35%
R = *p*-CF_3, 52%
R = *p*-OMe, 24%
R = *p*-NO_2, 34%
R = *m*-COOMe, 66%
R = *m*-OH, 55%
(R = *m*-BPin, 74%)
R = *o*-CF_3, 16%



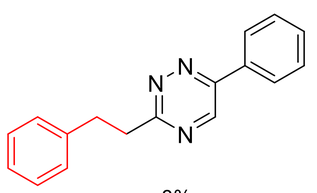
26%



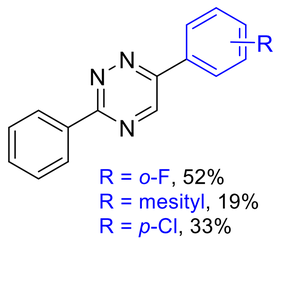
X = O, 37%
X = S, 66%



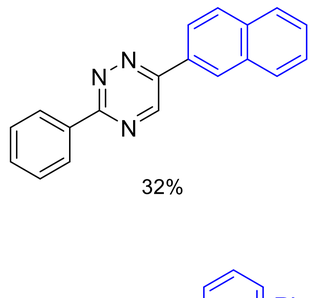
50%



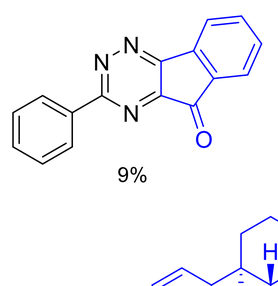
8%



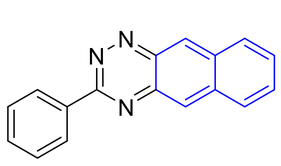
R = *o*-F, 52%
R = mesityl, 19%
R = *p*-Cl, 33%



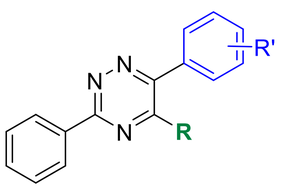
32%



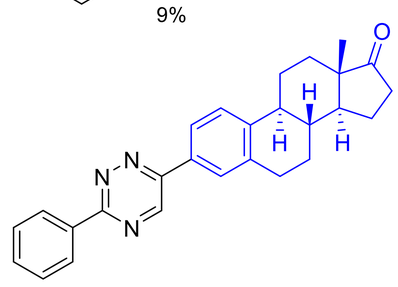
9%



26%



R = Me, R' = H, 40%
R = *i*Pr, R' = Cl, 16%



24%

Conclusions

A new method to access the 1,2,4-triazine scaffold is reported, via a telescoped reaction sequence using *N*-tosylhydrazones and aziridines. The approach represents a complementary alternative to well-known procedures and affords *3,6-disubstituted and 3,5,6-trisubstituted 1,2,4-triazines* in a regioselective manner as potentially useful compounds for *medicinal and agrochemical applications*.

Acknowledgements

This work was supported by a postdoctoral fellowship from Pfizer (L.C.), EPSRC Grants Nos. EP/K009494 and EP/M004120 (S.V.L.) and Erasmus Grants (L.B. and T.M.).

[1] (a) D. L. Boger, *Chem. Rev.*, **1986**, *86*, 781 (b) Y. F. Sainz, S. A. Raw, R. J. K. Taylor, *J. Org. Chem.*, **2005**, *70*, 10086 (c) M. Lorion, G. Guillaumet, J-F. Brière, F. Suzenet, *Org. Lett.*, **2015**, *17*, 3154.
[2] F. W. Lewis, L. M. Harwood, M. J. Hudson, A. Geist, V. N. Kozhevnikov, P. Distler, J. John, *Chem. Sci.*, **2015**, *6*, 4812.
[3] Agrochemical application: R. Braun, C. Waldraff, H. Dietrich, E. Gatzweiler, C. H. Rosinger, D. Schmutzler, PCT Int. Appl. **2014**, WO 2014053473 A1 20140410. Medicine applications: (a) K. Sztanke, K. Pasternak, B. Rajtar, M. Sztanke, M. Majek, M. Polz-Dacewicz, *Bioorg. Med. Chem.*,**2007**, *15*, 5480 (b) L. Yurttaş, S. Demirayak, S. Ilgın, O. Atlı, , *Bioorg. Med. Chem.*, **2014**, *22*, 6313-6323.
[4] (a) T. V. Saraswathi, V. R. Srinivasan *Tetrahedron Lett.,* **1971**, *25*, 2315 (b) D. S. Kopchuk, A. F. Khasanov, I. S. Kosalev, G. V. Zyryanov, V. L. Rusinov, O. N. Chupakhin *Medeleev Commun.* **2013**, *23*, 209 (c) D. S. Kopchuk, N. V. Chepchugov, G. A. Kim, G. V. Zyryanov, I. S. Kovalev, V. L. Rusinov, O. N. Chupakhin, *Tetrahedron Lett.* **2016**, *57*, 296.
[5] (a) Z. Zhao, W. H. Leister, K. A. Strauss, D. D. Wisnoski, C. W. Lindsley, *Tetrahedron Lett.*, **2003**, *44,* 1123. (b) T. Phucho, A. Nogpiur, S. Tumtin, R. Nongrum, B. Myrboh, R. L. Nongkhlaw, *ARKIVOC*, **2008**, *xv*, 79.
[6] L. Crespin, L. Biancalana, T. Morack, D. C. Blakemore, S. V. Ley, *Org. Lett*, **2017**, *19*, 1084.