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Highly substituted pyridines *via* tethered imine–enamine (TIE) methodology

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

Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: sar113@york.ac.uk. E-mail: rjkt1@york.ac.uk; Fax: +44(0)1904 434 523; Tel: +44(0)1904 432 606

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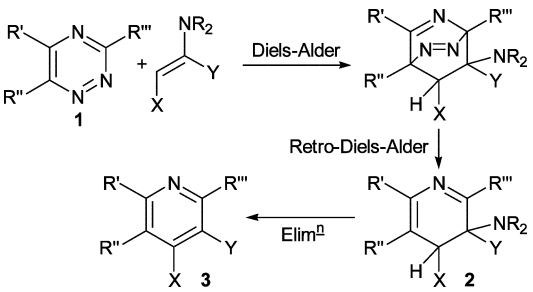
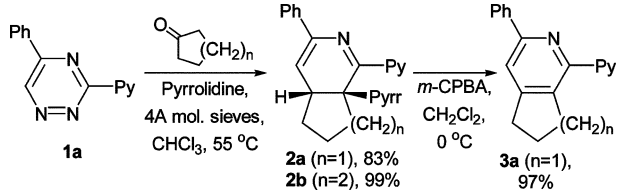
A tethered imine–enamine methodology has been developed for the direct conversion of 1,2,4-triazines into highly substituted pyridines *via* the inverse electron demand Diels–Alder reaction which avoids the need for a discrete aromatisation step. This TIE methodology has also been applied in one pot reaction cascades involving 1,2,4-triazines and utilising MnO_2-mediated tandem oxidation processes (TOPs).

The substituted pyridine motif is found in many biologically active compounds,[1] both naturally occurring and synthetic. As part of an ongoing research programme into the synthesis of heterocyclic and heteroaromatic compounds,[2] we were interested in the formation of highly substituted pyridines **3**. The inverse electron demand Diels–Alder reaction of 1,2,4-triazines with enamines appeared to be the method of choice (Scheme 1).[3]



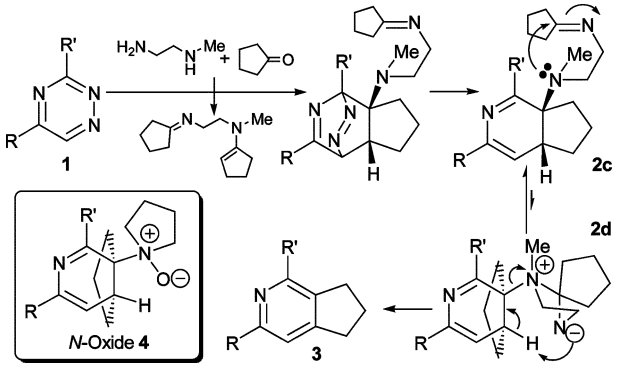
Scheme 1 Inverse demand Diels–Alder reaction of 1,2,4-triazines.

This methodology, widely used, has two main limitations, namely the requirement for a preformed enamine and the unusual stability of the intermediates **2** when using enamines derived from cyclohexanone.[3d] Boger *et al.*[3c–e] circumvented these difficulties for 1,2,4-triazine or 3-substituted-1,2,4-triazines: 4A molecular sieves allow *in situ* enamine formation and catalyse the elimination step forming pyridine **3** from dihydropyridine **2**, though yields remain low (19–66%). We found, however, that for our more substituted 1,2,4-triazines (*e.g.* **1a**), this procedure gave only the dihydropyridine intermediates (*e.g.* **2a** and **2b**), albeit in excellent yields (Scheme 2). No pyridine was observed in the ^{1}H NMR spectrum of the crude reaction products. Neither were pyridines **3a** or **3b** formed when the reactions were repeated in THF or toluene at reflux. Aromatisation of **2a** to **3a** was finally accomplished *via* Cope elimination of the corresponding *N*-oxide.[3a,4]



Scheme 2 Reaction of substituted 1,2,4-triazines with enamines.

Ideally, we required a procedure that could be applied to these more substituted 1,2,4-triazines **1** to allow the formation of the pyridines **3** in one transformation. We envisaged that the use of a tethered imine–enamine should provide an intermediate that mimics the *N*-oxide **4** (Scheme 3). The dihydropyridine **2c** can exist as zwitterion **2d**, which resembles the *N*-oxide **4**. We anticipated that **2d** would undergo elimination *in situ*, leading directly to the pyridine **3**.



Scheme 3 Tethered imine as a mimic of a Cope elimination intermediate.

N-Methylethylenediamine was chosen for several reasons: it is commercially available; the two carbon tether allows a 6-membered transition state (**2d**) and it provides the least hindered enamine possible. Hence, triazine **1a** in $CHCl_3$ was treated with cyclopentanone, *N*-methylethylenediamine and powdered 4A molecular sieves and heated to 55 °C or to reflux. Unfortunately, no reaction was observed by chromatographic analysis. However, when the reaction was repeated in toluene at reflux, the desired pyridine **3a** was obtained in an isolated yield of 74%.

The tethered imine–enamine concept vindicated, we went on to investigate the scope of this methodology, first with respect to the ketone (Table 1). As can be seen, cyclic ketones comprising small to medium-sized rings (from cyclopentanone to cyclooctanone) reacted with triazine **1a** to give the pyridines **3a–d** in good to quantitative yields (entries i–iv). Much larger rings, such as cyclododecanone, gave none of the desired pyridine even after extended reaction times, presumably due to steric factors.

The scope of this methodology was also explored in terms of the 1,2,4-triazine component. A range of triazines (**1b**,[5] **1c**,[6] **1d**[5] and **1e**) was synthesised according to literature procedures and all shown to be good substrates for this chemistry (entries v–ix). The use of trisubstituted triazine **1b** is of particular note in that the pentasubstituted pyridines **3e** (88%) and **3f** (82%) were formed with great efficiency (entries v and vi). The less active 3-heptadecyl-5-phenyl-1,2,4-triazine **1e** showed no conversion to the pyridine **3j** by chromatographic and spectroscopic analysis of the reaction mixture (entry x). Most interesting amongst these results, however, is the fact that cyclohexanone proved to be a useful substrate for the TIE methodology (entries ii, vi, viii), despite the intermediate dihydropyridines normally being reluctant to undergo aromatisation.[3c–e,4]

This TIE methodology also offers the possibilty of a catalytic variant.[3d,e] Thus, when **1b** was reacted under the standard conditions with just 20 mol% diamine for 72 h, pyridine **3e** was produced in a yield of 52% with 24% of **1b** being recovered. We are currently optimising this catalytic procedure.

We have recently published a MnO_2-mediated TOP (Tandem Oxidation Process) for the synthesis of nitrogen containing heterocyclic and heteroaromatic compounds.[2a] We were interested

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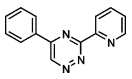
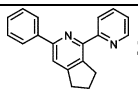
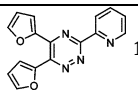
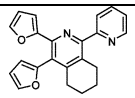
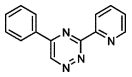
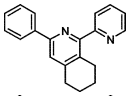
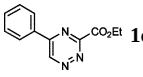
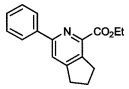
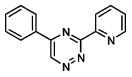
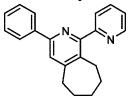
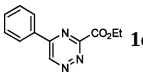
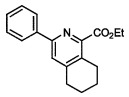
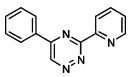
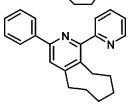
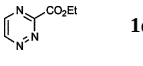
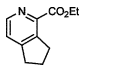
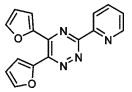
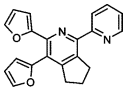
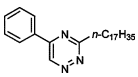
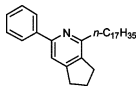
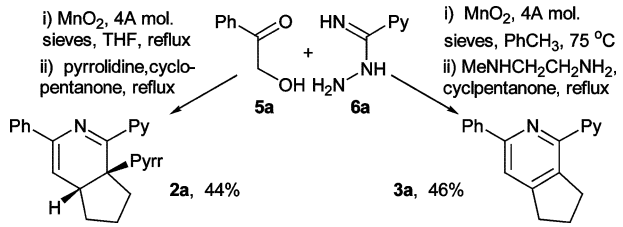
Table 1 Synthesis of highly substituted pyridines from 1,2,4-triazines[7,8]

Entry	Triazine	Ketone	Time	Product	Yield	Entry	Triazine	Ketone	Time	Product	Yield
i	 **1a**		22 h	 **3a**	74%	vi	 **1b**		21 h	 **3f**	82%
ii	 **1a**		36 h	 **3b**	79%	vii	 **1c**		6 h	 **3g**	33%
iii	 **1a**		22 h	 **3c**	100%	viii	 **1c**		16 h	 **3h**	61%
iv	 **1a**		21 h	 **3d**	77%	ix	 **1d**		16 h	 **3i**	31%
v	 **1b**		5 h	 **3e**	88%	x	 **1e**		36 h	 **3j**	—[a]

[a] ^{1}H NMR spectroscopy and chromatographic analysis of the crude reaction product showed only the triazine substrate in the aromatic region.

to examine whether such chemistry could be adapted to the TOP synthesis of 1,2,4-triazines **3** and, in particular, extended protocols which would allow the production of dihydropyridines (*e.g.* **2a**) and pyridines (*e.g.* **3a**) *in situ* from the corresponding amidrazone (*e.g.* **6a**) and α-hydroxyketone (*e.g.* **5a**). We are currently optimising this TOP–TIE chemistry but now disclose our preliminary results (Scheme 4). As can be seen, we have obtained good yields for these cascade reactions, the longest sequence being oxidation; double-condensation; Diels–Alder; retro-Diels–Alder; aromatisation to form **3a** in an overall yield of 46% from **5a**.



Scheme 4 TOP–TIE approaches to dihydropyridines and pyridines.

In conclusion, we have developed an improved protocol for the direct conversion of 1,2,4-triazines **1** into highly substituted pyridines **3** which eliminates the need for a second, discrete aromatisation step. The methodology is operationally simple and affords the pyridines **3** in good to quantitative yields. We have also adapted existing TOP methodology from our laboratories to the direct synthesis of dihydropyridine **2a** and pyridine **3a** from the amidrazone **6a** and the α-hydroxyketone **5a** *in situ* in good overall yields. We are currently employing the TIE methodology in target synthesis.

We are grateful the EPSRC for postdoctoral support (ROPA fellowship, S. A. R)

Notes and references

1 For examples see: M. S. Puar, A. K. Ganguly, A. Afonso, R. Brambilla, P. Mangiaracina, O. Sarre and R. D. MacFarlane, *J. Am. Chem. Soc.*, 1981, **103**, 5231; G. Beck, K. Kesseler, E. Baader, W. Bartmann, A. Bergmann, E. Granzer, H. Jendrella, B. v. Kerekjarto, R. Krause, E. Paulus, W. Schubert and G. Wess, *J. Med. Chem.*, 1990, **33**, 52; S. Ananthan, H. S. Kezzar III, R. L. Carter, S. K. Saini, K. C. Rice, J. L. Wells, P. Davis, H. Xu, C. M. Dersch, E. J. Bilsky, F. Porreca and R. B. Rothman, *J. Med. Chem.*, 1999, **42**, 3527; N. Oku, S. Matsunaga and N. Fusetani, *J. Am. Chem. Soc.*, 2003, **125**, 2044.

2 (*a*) S. A. Raw, C. D. Wilfred and R. J. K. Taylor, *Chem. Commun.*, 2003, 2286; (*b*) J. C. McManus, J. S. Carey and R. J. K. Taylor, *Synlett*, 2003, 365; (*c*) J. C. McManus, T. Genski, J. S. Carey and R. J. K. Taylor, *Synlett*, 2003, 369.

3 (*a*) H. Neunhoeffer, in *Comprehensive Heterocyclic Chemistry II*, vol. 6, ed. A. R. Katritzky, C. W. Rees and E. F. Scriven, 1996, Pergamon Press, Oxford, ch. 6.11; (*b*) D. L. Boger, *Tetrahedron*, 1983, **39**, 2869; (*c*) D. L. Boger and J. S. Panek, *J. Org. Chem*, 1981, **46**, 2179; (*d*) D. L. Boger, J. S. Panek and M. M. Meier, *J. Org. Chem*, 1982, **47**, 895; (*e*) D. L. Boger and J. S. Panek, *J. Am. Chem. Soc.*, 1985, **107**, 5745; (*f*) S. P. Stanforth, B. Tarbit and M. D. Watson, *Tetrahedron Lett.*, 2002, **43**, 6015; (*g*) E. C. Taylor and J. E. Macor, *J. Org. Chem.*, 1989, **54**, 1249; (*h*) Z. Wan and J. K. Snyder, *Tetrahedron Lett.*, 1997, **38**, 7495.

4 B. L. Chenard, R. T. Ronau and G. A. Schulte, *J. Org. Chem.*, 1988, **53**, 5175.

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6 S. C. Benson, J. L. Gross and J. K. Snyder, *J. Org. Chem.*, 1990, **55**, 3257.

7 **Representative procedure**: Synthesis of 3-phenyl-1-(2-pyridyl)-5,6,7,8-tetrahydroisoquinoline **3b**.[8] To a solution of 3-(2-pyridyl)-5-phenyl-1,2,4-triazine **1a** (0.10 mmol, 0.023 g) in toluene (1.0 mL) was added powdered 4A molecular sieves (0.100 g), cyclohexanone (0.60 mmol, 0.062 mL) and *N*-methylethylenediamine (0.30 mmol, 0.026 mL) and the mixture heated at reflux for 36 h. It was then cooled, filtered through a cotton wool plug and concentrated *in vacuo*, to furnish the crude product. Purification by column chromatography on silica gel (9 : 1 petrol ether : ethyl acetate) gave the title compound, **3b** (0.023 g, 79%) as a colourless oil: R_f 0.40 (3 : 1 petrol ether : ethyl acetate); ν_{max} (film) 3060, 2932, 2859, 1585, 1566, 1555, 1472, 1416, 1137, 799, 776, 746, 695 cm^{-1}; δ_H ($CDCl_3$) 1.64–1.85 (4 H, m), 2.78–2.92 (4 H, m), 7.17–7.42 (5H, m), 7.69–7.84 (2 H, m), 7.88–8.01 (2 H, m), 8.59 (1 H, dt, *J* 4.5 Hz, *J* 1.5 Hz, pyr-*H*6); δ_C ($CDCl_3$) 22.3 (CH_2), 23.3 (CH_2), 26.9 (CH_2), 30.0 (CH_2), 120.8 (CH), 122.6 (CH), 124.8 (CH), 126.9 (CH), 128.5 (CH), 128.7 (CH), 130.8. (C), 136.7 (CH), 139.7 (C), 148.2 (C), 148.3 (CH), 153.4 (C), 156.3 (C), 159.8 (C); *m*/*z* (CI) 287 (MH^+) [HRMS (CI) calcd. for $C_{20}H_{19}N_2$ 287.1548. Found 287.1544 (1.4 ppm error)].

8 All new compounds were fully characterised spectroscopically and by HRMS.