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Cascade Reactions of Substituted 1,2,4-Triazines: Rapid Access to Nitrogen-Containing Polycycles

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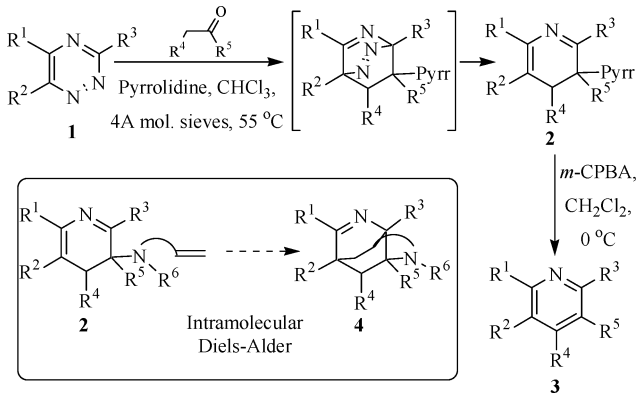
As part of our ongoing interest in the synthesis and utilization of nitrogen-containing heterocyclic and heteroaromatic compounds,[1] we had cause to explore the chemistry of 1,2,4-triazines **1**. The inverse electron demand Diels−Alder reactions of these aromatic compounds are well known,[2] and our research began with an investigation of Boger's in situ enamine protocol[3a,b] using polysubstituted triazines to prepare complex pyridines. We found that, in our systems, the Diels−Alder retro-Diels−Alder sequence, giving **2**, proceeded smoothly, but in situ aromatization was not observed and the dihydropyridines **2** were isolated in excellent yields[4] (Scheme 1); oxidation and Cope elimination were then employed to convert **2** into the corresponding pyridines **3**. To overcome this problem, we recently developed a novel tethered imine−enamine (TIE) methodology for the direct conversion of triazines **1** into highly substituted pyridines **3**.[5]

Scheme 1. Diels−Alder Reactions of 1,2,4-Triazine Systems

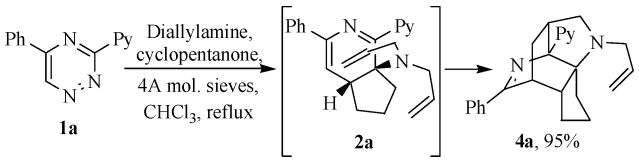


We also, however, have a long-standing research program into multistep in situ reactions[1a,b,6] and were therefore intrigued by the possibility that dihydropyridines of type **2** could be exploited in reaction cascades from 1,2,4-triazines **1**. The *s-cis*-2-azabutadiene moiety found in **2** is known to be a suitable substrate for Diels−Alder reactions.[2d,7] Our first foray into the cascade reactions of 1,2,4-triazines **1** was to investigate the trapping of the dihydropyridine intermediate **2** with an internal dienophile (Scheme 1). Such an approach would lead to a dramatic increase in molecular complexity: the planar triazine unit being amplified to a tricyclic system (e.g., **4**) with the formation of four new C−C bonds and five new stereogenic centers, with potential control of diastereoselectivity. We now report our initial results.

In the first instance, 1,2,4-triazine **1a** was allowed to react with cyclopentanone and diallylamine in $CHCl_3$ at reflux in the presence of powdered 4-Å molecular sieves. Formation of 7-allyl-(2-phenyl-10-(2-pyridyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene **4a** was observed in an excellent 95% isolated yield (Scheme 2).

In this multistep process, diallylamine and cyclopentanone react in situ to give the corresponding enamine, an electron-rich dienophile, as described by Boger et al.[3c] Inverse-electron-demand Diels−Alder reaction of this enamine with 1,2,4-triazine **1a**, an

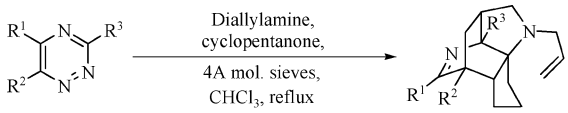
Scheme 2. Conversion of **1a** into Tetracycle **4a**



electron-deficient "diene", followed by immediate extrusion of nitrogen gives the dihydropyridine intermediate **2a**. Spontaneous intramolecular Diels−Alder reaction between one allyl moiety and the 2-azabutadiene unit then gives the desired tetracycle **4a**, with complete diastereoselectivity.[8] The observed regioselectivity of the initial Diels−Alder reaction is consistent with that reported for 3-substituted triazines.[2c]

With this result in hand, we went on to study the scope of the methodology, first with respect to the triazine **1** (Table 1). As can be seen, this chemistry is not limited to highly substituted systems, with mono-, di-, and trisubstituted triazines proving to be acceptable substrates. In all cases, the isolated yields are high and single isomers are obtained.

Table 1. Scope of Triazine Unit in Tetracycle Formation



Entry		R^1	R^2	R^3	Isolated yield
i	**1a**	Ph	H	2-Pyridyl	**4a,** 95%
ii	**1b**	2-Furyl	2-Furyl	2-Pyridyl	**4b,** 88%
iii	**1c**	Ph	H	CO_2Et	**4c,** 89%
iv	**1d**	H	H	CO_2Et	**4d,** 84%

The scope of this chemistry was also investigated with respect to the carbonyl unit. The disubstituted 1,2,4-triazine **1c** was allowed to react with a variety of ketones and aldehydes in the presence of diallylamine (Table 2). Again, the isolated yields are all high. Cyclic ketones with four-, five-, and six-membered rings work well (entries i−iii), as does a more substituted example, bicyclo[3.2.0]hept-2-en-6-one (entry iv), which gave the desired product in quantitative yield with complete diastereoselectivity. Finally, we showed that this methodology can be used on acyclic systems, valeraldehyde giving a single diastereomer (entry v).

In addition, *trans*-5-decenal also proved to be a viable acyclic carbonyl unit for this chemistry (Scheme 3). This example also shows that the intramolecular dienophile can be located elsewhere in the molecule, tricycle **4i** being isolated in 66% yield as a single diastereomer.

We then went on to examine the use of alternative amines in this chemistry (Table 3). As shown, a more complex allyl unit, such as *N*-methylgeranylamine, works well (entries i−iii). Conjugated alkenes have also been shown to be viable partners (entry

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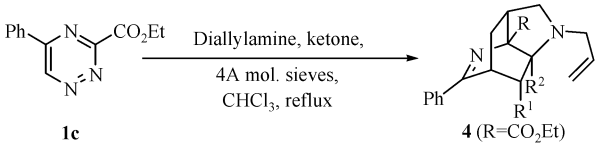
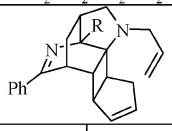
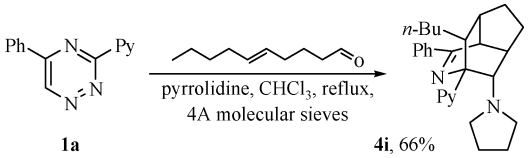
Table 2. Alternative Carbonyl Units in Tetracycle Formation



1c **4** (R=CO_2Et)

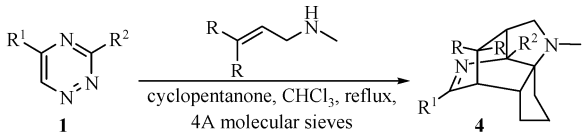
Entry	Ketone	R^1	R^2		Yield
i	cyclobutanone	-CH_2CH_2-		**4e**	100%
ii	cyclopentanone	-$CH_2CH_2CH_2$-		**4c**	89%
iii	cyclohexanone	-$CH_2CH_2CH_2CH_2$-		**4f**	86%
iv	bicyclo[3.2.0]hept -2-en-6-one			**4g**	100%
v	valeraldehyde	*n*-Pr	H	**4h**	92%

Scheme 3. Alternative Positioning of Intramolecular Dienophile

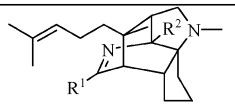
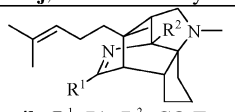
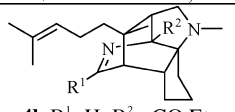
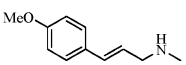
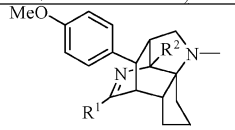


1a **4i**, 66%

Table 3. Alternative Amine Units in Tetracycle Formation



1 **4**

Entry	Triazine Amine	Product	Yield
i	**1a**, R^1=Ph R^2=2-Py	 **4j**, R^1=Ph R^2=2-Py	93%
ii	**1c**, R^1=Ph R^2=CO_2Et	 **4k**, R^1=Ph R^2=CO_2Et	91%
iii	**1d**, R^1=H R^2= CO_2Et	 **4l**, R^1=H R^2= CO_2Et	58%
iv	**1a**, R^1=Ph R^2=2-Py 	 **4m**, R^1=Ph R^2= 2-Py	87%

iv). These results are notable as the amines used contain one vinyl unit, compared to diallylamine with two, yet the efficiencies remain undiminished.

Finally, the structure of these polycyclic compounds **4** was confirmed by X-ray crystallography of **4j**, shown in Figure 1.[9]

In conclusion, we present an operationally simple method for the construction of complex polycyclic systems **4** in a cycloaddition cascade sequence from 1,2,4-triazines **1**. We have shown the flexibility of this chemistry by exploring its scope with respect to the triazine, carbonyl, and amine units involved in the reaction. The polycycles produced represent unusual scaffolds which may lend themselves to a variety of applications, for instance as ligands

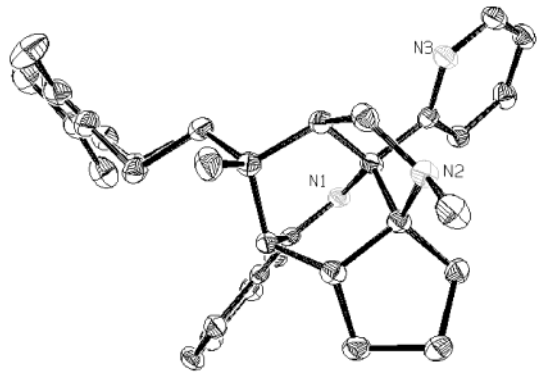


Figure 1. ORTEP diagram of **4j**. Hydrogen atoms have been omitted for clarity. Ellipsoids drawn at 50% probability. As shown, two orientations of the 4-methylpent-3-enyl unit were observed.

or chemotherapeutic agents. We are currently exploring enantioselective variants of this methodology[10] and their application to natural product and analogue synthesis.

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Supporting Information Available: Experimental procedures, data, and ^{1}H NMR spectra for **4a**−**m** (PDF); X-ray crystallographic data for **4j** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Org. Biomol. Chem.* **2004**, *2*, 788−796. (b) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Chem. Commun*. **2003**, 2286−2287. (c) McManus, J. C.; Carey, J. S.; Taylor, R. J. K. *Synlett* **2003**, 365−368. (d) McManus, J. C.; Genski, T.; Carey, J. S.; Taylor, R. J. K. *Synlett* **2003**, 369−371.

(2) For example, see: (a) Neunhoffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, Chapter 6.11, pp 507−573. (b) Neunhoffer, H In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, Chapter 2.19, pp 385−456. (c) Boger, D. L.; Weinreb, S. N. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: London, 1987; Chapter 10, pp 300−358. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869−2939.

(3) (a) Chenard, B. L.; Ronau, R. T. *J. Org. Chem.* **1988**, *53*, 5175−5177. (b) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179−2182. (c) Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895−897.

(4) The unusual stability of some dihydropyridines **2** to aromatization has been reported.[3]

(5) Raw, S. A.; Taylor, R. J. K. *Chem. Commun*. **2004**, 508−509.

(6) For examples, see: (a) Wei, X.; Taylor, R. J. K. *J. Org. Chem*. **2000**, *65*, 616−620. (b) Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Synlett* **2004**, 819−822. (c) Blackburn, L.; Kanno, H.; Taylor, R. J. K. *Tetrahedron Lett*. **2003**, *44*, 115−118. (d) Runcie, K. A.; Taylor, R. J. K. *Chem. Commun*. **2002**, 974−975. (e) Outram, H. S.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett*. **2002**, *43*, 6185−6187 and references therein.

(7) (a) Barluenga, J.; Tomas, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: London, 1993; Vol. 57, Chapter 1, pp 1−81. (b) Boger, D. L.; Weinreb, S. N. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: London, 1987; Chapter 9, pp 239−299.

(8) The structure of **4a**, and other key compounds, was assigned by extensive ^{1}H NMR spectroscopic analysis, including 2D techniques (COSY and NOESY). The bridgehead proton (H-1) normally appears as a distinctive broad singlet (δ 2.7−3.5 ppm) in ^{1}H NMR and can be used as a reference in 2D NMR to identify other signals (see Supporting Information). Final proof of the structure of tetracycles **4** was found when an X-ray crystal structure of **4j** was obtained.

(9) The CCDC 244632 contains the supplementary crystallographic data for compound **4j**. These can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk.

(10) So far we have explored the use of amides derived from triazine **1c** and chiral amines. The best de obtained to date was 10%, using the amide synthesized from **1c** and (1*R*,2*R*)-2-benzyloxycyclopentylamine.

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