The preparation of highly substituted pyridazines *via* a tethered imine-enamine (TIE) procedure

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Abstract
1,2,4,5-Tetrazines can be converted directly into cyclo-annelated pyridazines *via* an inverse electron demand Diels-Alder procedure incorporating tethered imine-enamine (TIE) methodology. This methodology provides an improved one-pot preparation of such compounds, eliminating the need for either the preformation of the enamine or a separate aromatisation step, and has been applied to 4 tetrazines producing 11 pyridazines.

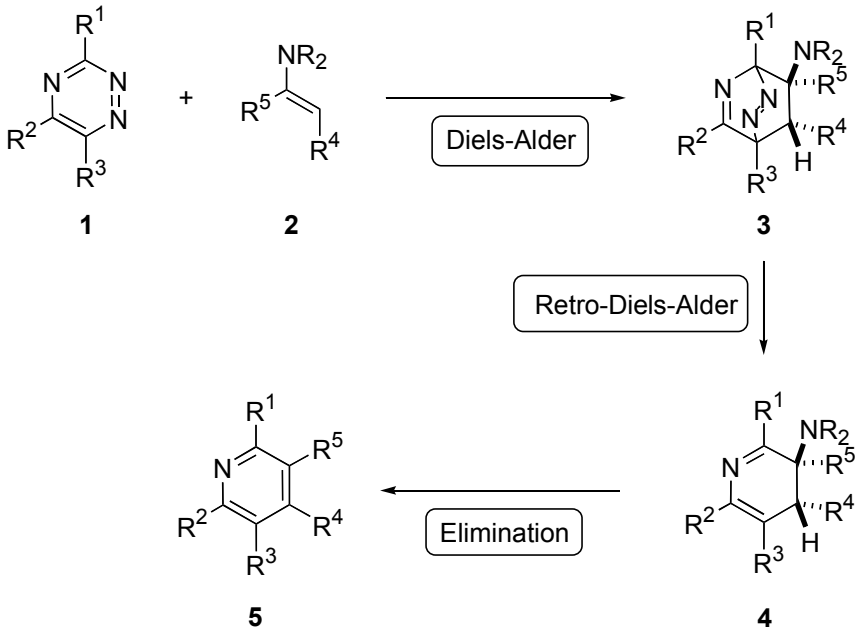
Keywords: 1,2,4,5-Tetrazines, pyridazines, inverse electron demand Diels-Alder

Introduction

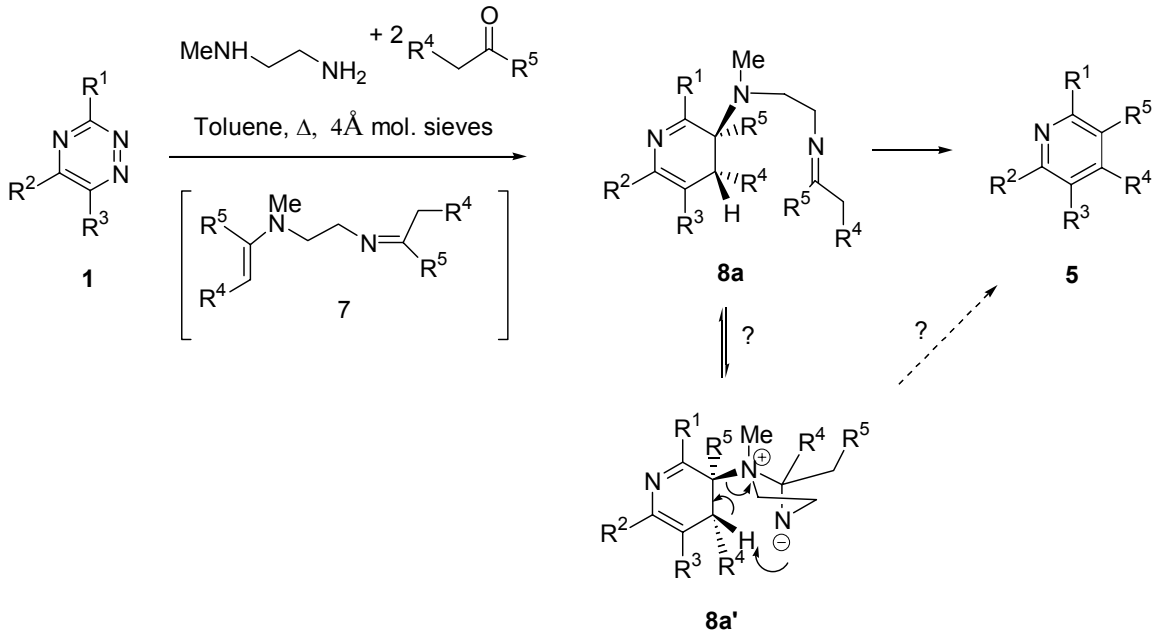
The inverse electron demand Diels-Alder reaction of 1,2,4-triazines **1** with enamines **2** has been previously utilised to prepare a range of substituted pyridines **5** (Scheme 1).[1-5] This procedure was greatly improved by Boger *et al.* who developed modifications which enabled the enamine **2** to be prepared *in situ*.[2] With more substituted examples, however, the final elimination/aromatisation step of intermediate **4** can prove problematic and a separate oxidation/Cope elimination may be required to complete the sequence.[2b,3,4]

To overcome this problem, we developed the tethered-imine-enamine (TIE) procedure shown in Scheme 2.[4] Thus, *N*-methylethylenediamine on treatment with two equivalents of a ketone *in situ* produces imine-enamine **7** which, after reaction with 1,2,4-triazine **1** and subsequent retro-Diels-Alder reaction, generates the tethered imine **8a**. We envisage the imine acting as a tethered base to facilitate conversion into the corresponding pyridine **5** by promoting an E1cb mechanism or epimerising adjacent to the amine leaving group to enable an *anti*-elimination to take place. We also conjectured that the zwitterionic species **8a'** could be present to some extent thus enhancing the basic nature of the tethered imine (and mimicking the *N*-oxide intermediate in the Cope elimination).

[†] Richard Taylor was Chairman of the RSC Heterocyclic Group during the period 1999-2001



Scheme 1



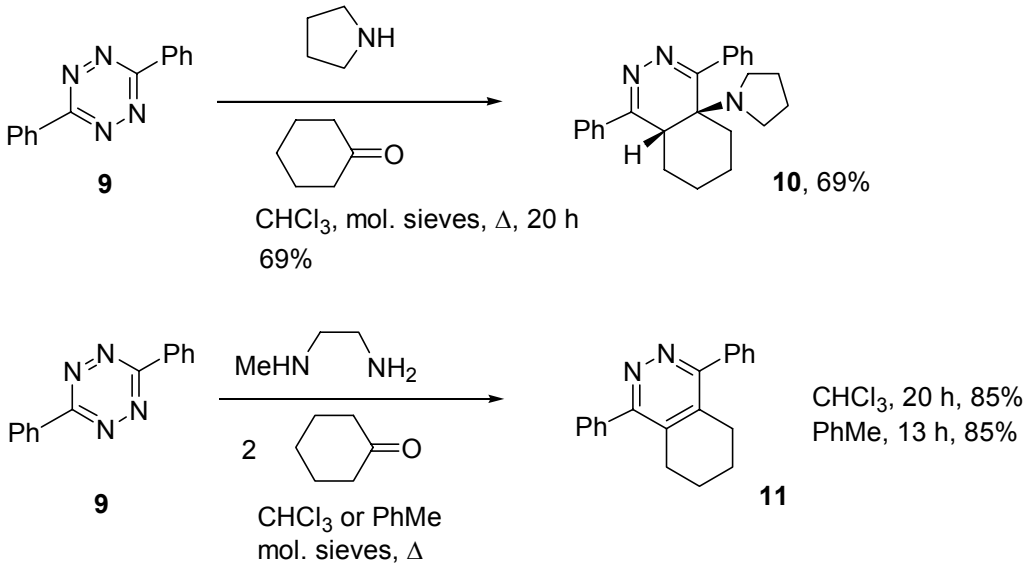
Scheme 2

Whatever the validity of the mechanistic speculation shown in Scheme 2, the TIE procedure was successfully utilised to prepare a wide range tri-, tetra- and penta-substituted

pyridines **5** in high yields.[4] In this paper, we report on the extension of the TIE procedure to the preparation of pyridazines from substituted-1,2,4,5-tetrazines.

Results and Discussion

Inverse electron demand Diels-Alder reactions of 3,6-disubstituted-1,2,4,5-tetrazines have received considerable attention,[1,5] although reactions with enamines derived from cycloalkanones, leading to pyridazines have been less well explored.[5b,5c,5h] In order to evaluate the usefulness of the TIE methodology in this area, our first objective was to compare the TIE methodology with standard Boger *in situ* enamine procedure (Scheme 3). Thus, when the one-pot reaction of commercially available diphenyltetrazine **9** with the enamine formed from cyclohexanone and pyrrolidine was carried out, the non-aromatised adduct **10** was obtained as the sole product in 69% yield. Application of the TIE procedure, that is treatment of tetrazine **9** with *N*-methylethylenediamine and two equivalents of cyclohexanone, resulted in the direct formation of pyridizine **11**, in a yield of 85% (Scheme 3). Further optimisation studies indicated that the molecular sieves were not required and that the use of an excess of *N*-methylethylenediamine (3 equiv.) and ketone (6 equiv.) sometimes gave improved yields - -these conditions were therefore adopted as standard.

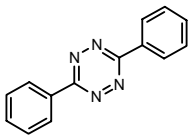
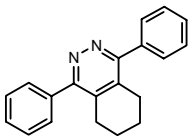
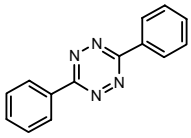
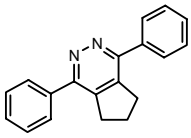
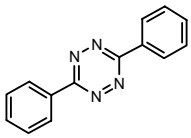
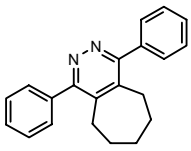
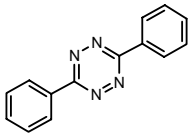
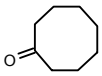
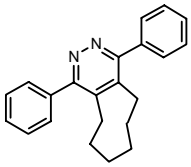
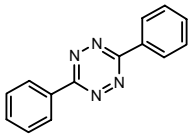
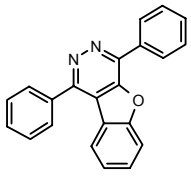


Scheme 3

Having successfully prepared pyridazine **11** in a one-step procedure, and having once again demonstrated the efficiency of the TIE procedure in the aromatisation step, we went on to explore the scope of the reaction with respect to the ketone (Table 1). It was established that tetrazine **9** reacts efficiently with a range of cyclic ketones from cyclopentanone to

cyclooctanone giving the corresponding pyridazines **11-14** in high yields (85-97%, entries i-iv) under TIE conditions, a considerable improvement over the published[5h,6] procedure in terms of both operational simplicity and yields. Tetrazine **9** also underwent reaction with 3-coumaranone to give pyridazine **15** in 95% yield by a one-pot process (entry v): the reported[5c] procedure for the preparation of **15,** not only requires preformation of the enamine (derived from pyrrolidine and 3-coumaranone), but also requires a second aromatisation step, giving **15** in a 60% overall yield.

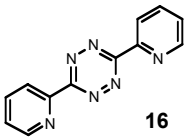
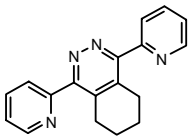
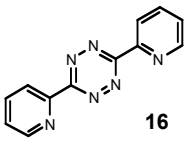
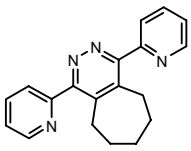
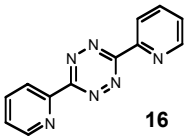
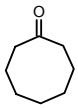
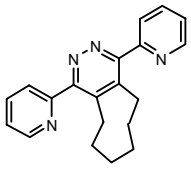
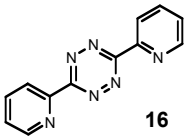
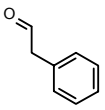
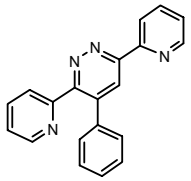
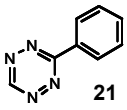
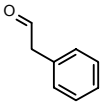
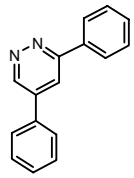
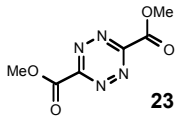
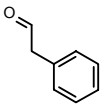
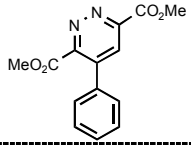
Table 1. Reactions of 3,6-diphenyl-1,2,4,5-tetrazine (**9**) with ketones (6.0 equiv.) and N-methylethylenediamine (3.0 equiv.) in refluxing toluene

Entry	Tetrazine **9**	Ketone	Time	Product		Yield
i			13 h		**11**	85%
ii			1.5 h		**12**	93%
iii			1.5 h		**13**	97%
iv			12 h		**14**	89%
v			2 h		**15**	95%

Having successfully demonstrated the TIE procedure to be an improved method for the direct conversion of tetrazine **9** into highly substituted pyridazines, we went on to explore the scope of the reaction in terms of the tetrazine (Table 2). Atfah has reported the reaction of commercially available 3,6-di-2-pyridyl-1,2,4,5-tetrazine (**16**) with the enamines derived from cyclohexanone, cycloheptanone and cycloctanone but utilising a three-step synthesis (enamine

formation, cycloaddition and aromatisation).[5h] The requirement for a discrete aromatisation step provided an opportunity to apply our TIE procedure to this more challenging substrate. As can be seen (entries i-iii), pyridazines **17**-**19** were obtained in yields of 41%, 71% and 30%, respectively, via the one-pot process using refluxing xylene as solvent (the yields in toluene were considerably lower). The reaction of tetrazine **16** with cyclopentanone and *N*-methylethylenediamine, failed to give corresponding pyridazine product.

Table 2. Reactions of tetrazines with carbonyl compounds (6.0 equiv.) and *N*-methylethylenediamine (3.0 equiv.)

Entry	Tetrazine	Carbonyl	Time	Product		Yield
i	 **16**		1 h		**17**	41%[a]
ii	 **16**		2 h		**18**	71%[a]
iii	 **16**		1 h		**19**	30%[a]
iv	 **16**		5 min		**20**	90%[b]
v	 **21**		3 min		**22**	86%[b]
vi	 **23**		5 min		**24**	80%[b,c]

[a]In refluxing xylene (yields in PhMe at reflux were **17** (25%), **18** (35%), **19** (15%)).
[b]In PhMe at reflux.
[c]Using 2 equiv. of aldehyde and 1 equiv. of diamine.

Finally, we went on to extend the TIE procedure to the one-pot preparation of pyridazines **20**, **22** and **24** from tetrazines **16, 21**[7] and **23**[8] and phenylacetaldehyde (Table 2, entries iv-vi). In these examples, the reactions were complete in 3-5 minutes on being heated in toluene. In the case of tetrazine **21** (entry v), pyridazine **22** was obtained with complete regioselectivity (as indicated by ^{1}H NMR spectroscopy [δ 8.00 ppm (1 H, d, J = 2.0 Hz) and 9.42 ppm (1 H, d, J = 2.0 Hz)].[10]

In summary, we have successfully extended the TIE methodology to prepare di-, tri- and tetra-substituted pyridazines, some annelated, from the corresponding 1,2,4,5-tetrazines in a one-pot process. This procedure does not require the use of pre-formed enamines, or a separate aromatisation step, and in many examples gives almost quantitative yields of the pyridazine products.

Experimental Section

General Procedures. Tetrazines **21**[7] and **23**[8] were prepared according to literature procedures. All other reagents and solvents were of commercial grade. NMR spectra were recorded on Jeol EX270 or Jeol ECX400 instruments and were recorded in $CDCl_3$. Melting points were determined on a Gallenkamp melting point apparatus.

General experimental procedure

To a solution of tetrazine (1 equiv.) in toluene or xylene (see Tables, 2 mL) was added the carbonyl compound (6 equiv.) and *N*-methylethylenediamine (3 equiv.). The mixtures were heated at reflux for the specified time then allowed to cool and concentrated *in vacuo*. Pyridazines **11**-**15**, **22** and **24** were purified by flash chromatography on silica (dichloromethane-ethyl acetate, 9:1), whereas pyridazines **17**-**20** were purified by flash chromatography on alumina (deactivated with 6% H_2O w/w) (dichloromethane-ethyl acetate, 8:2 for **17**-**19** and 1:1 for **20**).

5,6,7,8-Tetrahydro-1,4-diphenylphthalazine (11). After 13 h at reflux using the general procedure, 3,6-diphenyl-1,2,4,5-tetrazine **9** (50 mg, 0.21 mmol), cyclohexanone (133 μL, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **11** (51 mg, 85%) as a white solid, m.p. 172-174 ^{o}C (Lit.[5h] m.p. 172-174 ^{o}C) displaying consistent spectroscopic data.

6,7-Dihydro-1,4-diphenyl-5*H*-cyclopenta[*d*]pyridazine (12). After 1.5 h at reflux using the general procedure, 3,6-diphenyl-1,2,4,5-tetrazine **9** (50 mg, 0.21 mmol), cyclopentanone (113 μl, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **12** (53 mg, 93%) as a white solid, m.p: 160-161 ^{o}C (Lit.[5h] m.p. 161-163 ^{o}C) displaying consistent spectroscopic data.

6,7,8,9-Tetrahydro-1,4-diphenyl-5*H*-cyclohepta[*d*]pyridazine (13). After 1.5 h at reflux using the general procedure, 3,6-diphenyl-1,2,4,5-tetrazine **9** (50 mg, 0.21 mmol), cycloheptanone (151 μL, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **13**

(61 mg, 97%) as a white solid, m.p. 152-155 °C (Lit.[5h] m.p. 152-154 °C) displaying consistent spectroscopic data.

5,6,7,8,9,10-Hexahydro-1,4-diphenyl-cycloocta[*d*]pyridazine (14). After 12 h at reflux using the general procedure, 3,6-diphenyl-1,2,4,5-tetrazine **9** (50 mg, 0.21 mmol), cyclooctanone (168 μL, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **14** (59 mg, 89%) as a white solid, m.p. 163-165 °C (Lit.[5h] m.p. 163-165 °C) displaying consistent spectroscopic data.

1,4-Diphenyl[1]benzofuro[2,3-d]pyridazine (15). After 2 h at reflux using the general procedure, 3,6-diphenyl-1,2,4,5-tetrazine **9** (30 mg, 0.13 mmol), 3-coumaranone (104 mg, 0.78 mmol) and *N*-methylethylenediamine (49 μL, 0.57 mmol) gave the title compound **15** (40 mg, 95%) as a white solid, m.p. 157-158 °C (Lit.[5c] m.p. 157-158 °C) displaying consistent spectroscopic data.

5,6,7,8-Tetrahydro-1,4-di-(2-pyridyl)phthalazine (17). After 1 h at reflux using the general procedure, 3,6-di-2-pyridyl-1,2,4,5-tetrazine **16** (50 mg, 0.21 mmol), cyclohexanone (133 μL, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **17** (25 mg, 41%) as a sticky yellow film with spectroscopic data in accord with those published.[5h]

6,7,8,9-Tetrahydro-1,4-di-(2-pyridyl)-5*H*-cyclohepta[*d*]pyridazine (18). After 2 h at reflux using the general procedure, 3,6-di-2-pyridyl-1,2,4,5-tetrazine **16** (50 mg, 0.21 mmol), cycloheptanone (151 μL, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **18** (45 mg, 71%) as a white solid, m.p. 130-131 °C (Lit.[5h] m.p. 129-130 °C) displaying consistent spectroscopic data.

5,6,7,8,9,10-Hexahydro-1,4-(di-2-pyridyl)cycloocta[*d*]pyridazine (19). After 1 h at reflux using the general procedure, 3,6-di-2-pyridyl-1,2,4,5-tetrazine **16** (50 mg, 0.21 mmol), cyclooctanone (168 μL, 1.28 mmol) and *N*-methylethylenediamine (56 μL, 0.64 mmol) gave the title compound **19** (20 mg, 30%) as a white solid, m.p. 161-163 °C (Lit.[5h] m.p. 161-163 °C) displaying consistent spectroscopic data.

4-Phenyl-3,6-di-(2-pyridyl)pyridazine (20). After 5 min at reflux using the general procedure, 3,6-di-2-pyridyl-1,2,4,5-tetrazine **16** (30 mg, 0.13 mmol), phenylacetaldehyde (89 μL, 0.76 mmol) and *N*-methylethylenediamine (33 μL, 0.38 mmol) gave the title compound **20** (35 mg, 90%) as light yellow solid, m.p. 176-178 °C (Lit.[9] m.p: 177.5-178.5 °C) displaying consistent spectroscopic data.

3,5-Diphenylpyridazine (22). After 3 min at reflux using the general procedure, 3-phenyl-1,2,4,5-tetrazine **21** (30 mg, 0.19 mmol), phenylacetaldehyde (133 μL, 1.14 mmol) and *N*-methylethylenediamine (33 μL, 0.38 mmol) gave the title compound **22** (38 mg, 86%) as a light yellow solid, m.p. 136-139 °C (Lit.[10] m.p: 137 °C) displaying consistent spectroscopic data.

Dimethyl 4-phenylpyridazine-3,6-dicarboxylate (24). After 5 min at reflux using the general procedure, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **23** (30 mg, 0.15 mmol), phenylacetaldehyde (35 μL, 0.30 mmol) and *N*-methylethylenediamine (13 μL, 0.15 mmol) gave the title compound **25** (33 mg, 80%) as a yellow oil with spectroscopic data in accord with those published.[5f] [N.B. a 58% yield was obtained using the standard 1:6:3 ratio of reactants due to

purification problems; the use of a 1:2:1 ratio of reactants was successful due to the rapid rate of reaction].

Acknowledgements

We are grateful to the EPSRC for postgraduate (P.H.G.) and postdoctoral (S.A.R.) funding.

References

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