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. 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, although reactions with enamines derived from cycloalkanones, leading to pyridazines have been less well explored. 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 pyridazine 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](image)

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 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 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tetazine 9</th>
<th>Ketone</th>
<th>Time</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td><img src="image" alt="Tetrazine 9" /></td>
<td><img src="image" alt="Ketone" /></td>
<td>13 h</td>
<td><img src="image" alt="Product" /></td>
<td>85%</td>
</tr>
<tr>
<td>ii</td>
<td><img src="image" alt="Tetrazine 9" /></td>
<td><img src="image" alt="Ketone" /></td>
<td>1.5 h</td>
<td><img src="image" alt="Product" /></td>
<td>93%</td>
</tr>
<tr>
<td>iii</td>
<td><img src="image" alt="Tetrazine 9" /></td>
<td><img src="image" alt="Ketone" /></td>
<td>1.5 h</td>
<td><img src="image" alt="Product" /></td>
<td>97%</td>
</tr>
<tr>
<td>iv</td>
<td><img src="image" alt="Tetrazine 9" /></td>
<td><img src="image" alt="Ketone" /></td>
<td>12 h</td>
<td><img src="image" alt="Product" /></td>
<td>89%</td>
</tr>
<tr>
<td>v</td>
<td><img src="image" alt="Tetrazine 9" /></td>
<td><img src="image" alt="Ketone" /></td>
<td>2 h</td>
<td><img src="image" alt="Product" /></td>
<td>95%</td>
</tr>
</tbody>
</table>

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 cyclooctanone but utilising a three-step synthesis (enamine
formation, cycloaddition and aromatisation). 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.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tetrazine</th>
<th>Carbonyl</th>
<th>Time</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td><img src="16" alt="Image" /></td>
<td><img src="17" alt="Image" /></td>
<td>1 h</td>
<td><img src="17" alt="Image" /></td>
<td>41%a</td>
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<tr>
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<td><img src="18" alt="Image" /></td>
<td>2 h</td>
<td><img src="18" alt="Image" /></td>
<td>71%a</td>
</tr>
<tr>
<td>iii</td>
<td><img src="16" alt="Image" /></td>
<td><img src="19" alt="Image" /></td>
<td>1 h</td>
<td><img src="19" alt="Image" /></td>
<td>30%a</td>
</tr>
<tr>
<td>iv</td>
<td><img src="16" alt="Image" /></td>
<td><img src="20" alt="Image" /></td>
<td>5 min</td>
<td><img src="20" alt="Image" /></td>
<td>90%b</td>
</tr>
<tr>
<td>v</td>
<td><img src="21" alt="Image" /></td>
<td><img src="22" alt="Image" /></td>
<td>3 min</td>
<td><img src="22" alt="Image" /></td>
<td>86%b</td>
</tr>
<tr>
<td>vi</td>
<td><img src="23" alt="Image" /></td>
<td><img src="24" alt="Image" /></td>
<td>5 min</td>
<td><img src="24" alt="Image" /></td>
<td>80%b,c</td>
</tr>
</tbody>
</table>

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 and 23 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 [$\delta$ 8.00 ppm (1 H, d, $J$ = 2.0 Hz) and 9.42 ppm (1 H, d, $J$ = 2.0 Hz)].

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 and 23 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$_2$O 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 $\mu$L, 1.28 mmol) and $N$-methylethylenediamine (56 $\mu$L, 0.64 mmol) gave the title compound 11 (51 mg, 85%) as a white solid, m.p. 172-174 °C (Lit. 5h m.p. 172-174 °C) displaying consistent spectroscopic data.

**6,7-Dihydro-1,4-diphenyl-5H-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 $\mu$L, 1.28 mmol) and $N$-methylethylenediamine (56 $\mu$L, 0.64 mmol) gave the title compound 12 (53 mg, 93%) as a white solid, m.p: 160-161 °C (Lit. 5h m.p. 161-163 °C) displaying consistent spectroscopic data.

**6,7,8,9-Tetrahydro-1,4-diphenyl-5H-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 $\mu$L, 1.28 mmol) and $N$-methylethylenediamine (56 $\mu$L, 0.64 mmol) gave the title compound 13 (53 mg, 93%) as a white solid, m.p: 172-174 °C (Lit. 5h m.p. 172-174 °C) displaying consistent spectroscopic data.
(61 mg, 97%) as a white solid, m.p. 152-155 °C (Lit. 5th 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. 5th 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)-5H-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. 5th 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. 5th 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

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References

6. The reaction between tetrazine 9 and cycloheptanone to give pyridazine 13 (Table 1, entry iii) was also carried out using morpholine in refluxing toluene and a yield of 80% (5 h) was obtained. With the preformed enamine the yield was almost quantitative (but was only reported5h to be 42%). These results indicate that the yields in Aftah’s publication (ref. 5h) may all be capable of improvement when carried out as one-pot processes (although the TIE procedure is still the preferred method).