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Tandem 'Inverse Electron-Demand' Diels-Alder Reactions of Dienamines with a 1,2,4,5-Tetrazine. A New Azo-Bridged Ring System

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Abstract: Reaction of (*EE*)-1-morpholino-2-methylpenta-1,3-diene **1a** with dimethyl 1,2,4,5-tetrazine-3,6-di-carboxylate **2** in acetonitrile solution gives dimethyl 2,5-dimethyl-3-morpholino-8,9-diaza-tricyclo[2.2.2.$0^{2,6}$]oct-8-ene-1,4-dicarboxylate **4a**, in high yield (79%) and with high apparent diastereoselectivity; the 1-(4-methylpiperazino) analogue **1b** similarly gives compound **4b** (66%). Compounds **4a** and **4b** are the first recorded representatives of this bridged tricyclic ring system. In contrast 2-methyl-1-morpholinocyclopentadiene **5** reacts with 2 mol. equiv. of the tetrazine **2**, giving the cyclopentadipyridazine **6**.

The 'inverse electron-demand' Diels-Alder reaction of 1,2,4,5-tetrazines with alkynes and alkenes provides a useful synthetic route to certain substituted pyridazines.[1] When alkynes are used, pyridazines (and nitrogen) are produced directly, whereas the reactions involving alkenes give initially dihydropyridazines which are rarely isolated but are transformed into the corresponding pyridazines by oxidation or elimination. In the case of some extremely reactive dienophiles, e.g. cyclopropene,[2] cyclobutadiene,[3] or benzvalene,[4] the intermediate dihydropyridazines, which are themselves electron-deficient azadienes, may undergo a second Diels-Alder reaction giving polycyclic products.

Little attention has so far been paid to the reactions of 1,2,4,5-tetrazines with conjugated dienes. The only literature report of a double addition[5] involves the reaction of two molecules of diaryltetrazines with 1-(dialkylamino)butadienes: however, the bis-(dihydropyridazines) then undergo oxidative carbon-carbon bond cleavage to give pyridazines in low yield. Hetaryldienamines and hetaryldienol ethers generally react with 1,2,4,5-tetrazines in the manner of normal enamines and enol ethers,[6] giving hetarylvinylpyridazines,[7,8] products which do not apparently react further with an excess of the tetrazine.

As part of a study of the 'inverse electron-demand' Diels-Alder reactions of mono- and bis-1,2,4,5-tetrazines with mono- and bi-functional dienophiles,[9] we are currently investigating the reactions of a number of conjugated dienamines with simple tetrazines. We now report that two of the model compounds, (*EE*)-1-morpholino-2-methylpenta-1,3-diene **1a**[10] and (*EE*)-1-(4-methylpiperazino)-2-methylpenta-1,3-diene **1b**[10] react smoothly at ambient temperature with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **2**[11] in acetonitrile to give high yields (79 and 66% respectively) of the colourless tricyclic diesters **4a** and **4b** (Scheme 1). The structure of compound **4a** has been established by X-ray crystallography (Fig.1), and the structural relationship between **4a** and **4b** has been established by ^{1}H and ^{13}C NMR spectroscopy.

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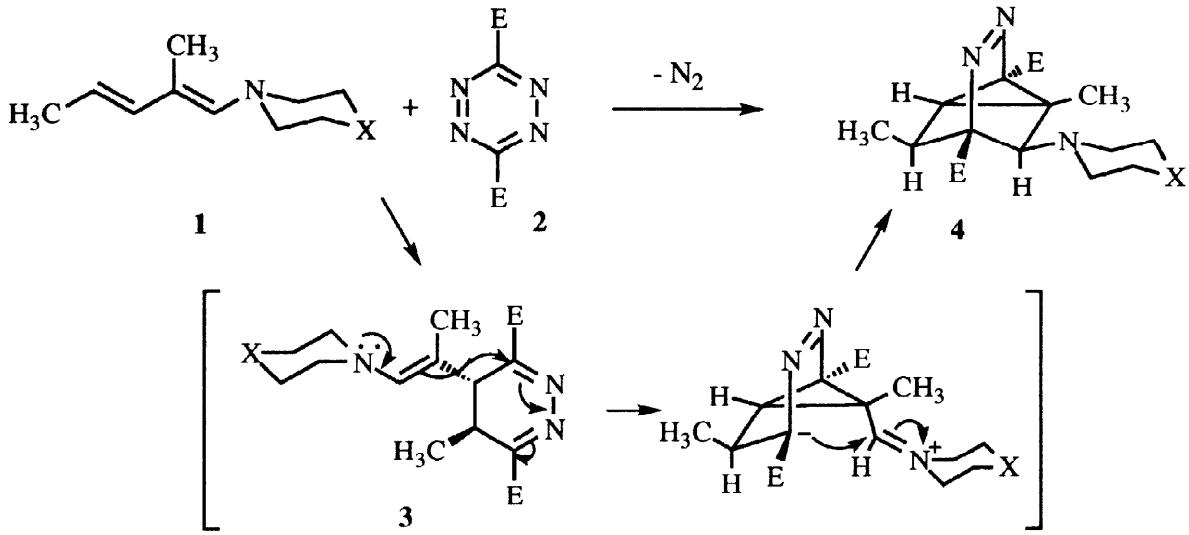
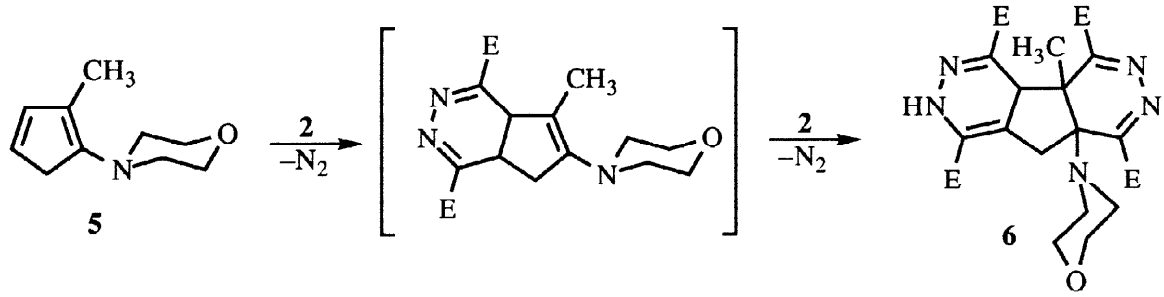
These reactions constitute the first recorded syntheses of the 8,9-diazatricyclo[2.2.2.$0^{2,6}$]oct-8-ene ring system. We believe that the most plausible mechanistic rationalisation involves as the first step the cycloaddition of the tetrazine to the less hindered 3,4-double bond of the dienamine to give the dihydropyridazine **3a** or **3b**, followed by the intramolecular addition of the reactive enamine moiety to the diene system of the latter. It is not yet clear whether this second stage is best represented as a concerted cycloaddition, or the stepwise process shown in Scheme 1, although it should be noted that only one diastereomer is apparently produced. In any case, the intramolecular step is evidently very fast, since the intermediates **3a** and **3b** might otherwise lose their stereochemical homogeneity through tautomeric equilibria within the dihydropyridazine moiety.[7] The relative stereochemistry of the substituents in the tricycles **4a** and **4b** is consistent with the stereochemistry of the starting dienamines (their structures were verified by nOe measurements) and with the proposed reaction mechanism.





Scheme 1

In an attempt to fix the *cisoid* geometry of the diene and thus set up the alignment of the double bonds for a tandem cycloaddition, 2-methyl-1-morpholinocyclopentadiene **5**[12] was allowed to react with the tetrazine-dicarboxylic ester **2**. However, in this case the only isolated product (42%) was identified as the cyclopentadipyridazine **6**, a product arising from the addition of *two* equivalents of the tetrazine **2** to the diene. Assignment of the structure as **6**, rather than an alternative tautomer, is based on IR (N-H stretching at 3567 and 3368 cm^{-1}), ^{1}H and ^{13}C NMR spectra, and on analogy with the work of Seitz[13] and Neunhoeffer[14]. The absence

of any product of a tandem reaction suggests that in this case the geometrical strain arising in an intramolecular second step makes this pathway unfavourable relative to the double addition.

Attempts to define the scope and limitations of this novel tandem cyclisation process are now in progress.

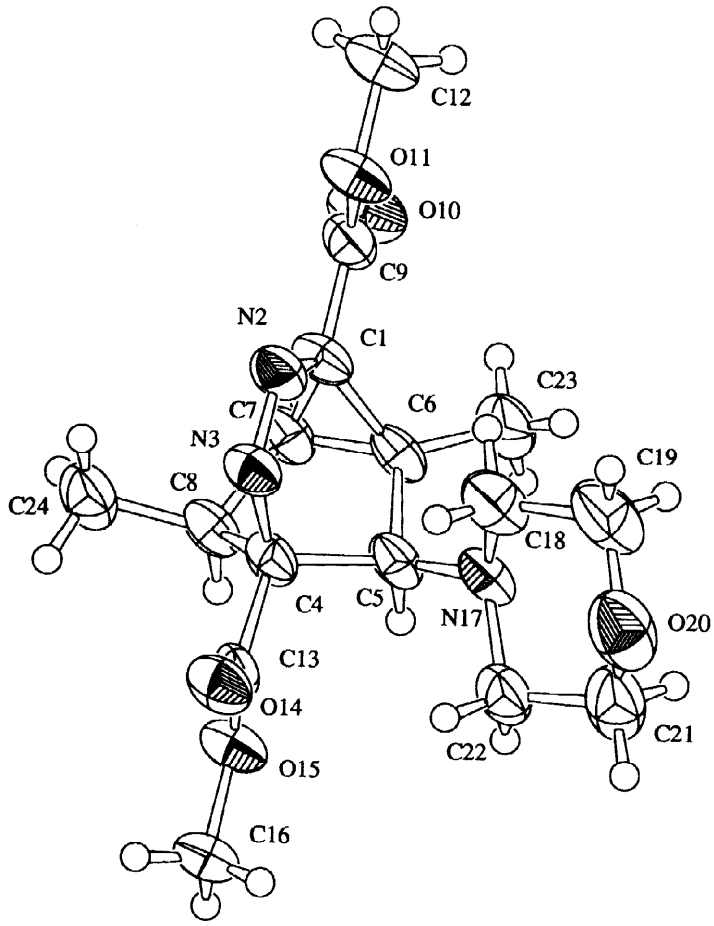


Fig. 1. X-Ray crystal structure of compound **4a**

[The non-standard atom numbering corresponds to that used in the deposited crystallographic data.]

General procedure: The diester **2** (1 mmol) in acetonitrile (20 cm^3) was added over 2 h to the solution of the dienamine (1 mmol) in acetonitrile (10 cm^3). The mixture was left overnight at ambient temperature; the solvent was then evaporated and the residue recrystallised from ethyl acetate.

***Analytical data for compound* 4a:** mp 140-142°C (dec.). Found: C, 57.1; H, 6.7; N, 12.4. $C_{16}H_{23}N_3O_5$ requires C, 56.95; H, 6.9; N., 12.5%. δ_H (500 MHz, $CDCl_3$) 0.42 (3H, d, *J* 6.7 Hz), 1.33 (3H, s), 2.25 (4H, br s), 2.58 (1H, s), 2.63 (1H, q, *J* 6.7 Hz), 3.44-3.53 (4H, m), 3.58 (1H, s) and 4.01 (6H, s). δ_C (125 MHz) 11.1, 11.2, 34.4, 37.3, 37.4, 50.6, 53.4†, 62.5, 67.5, 67.6, 81.0, 169.2 and 172.6. *m/z* 337 ($M^{+\cdot}$, 22%), 251 (100), 152 (31), 93 (56), 57 (58).

***Crystal data for compound* 4a:** $C_{16}H_{23}N_3O$: *M* 337.37; triclinic, space group $P\bar{1}$, *a* = 10.030(8), *b* = 14.614(7), *c* = 5.852(7)Å, a = 98.93(6)°, b = 90.65(8)°, g = 103.13(4)°, V = 824(1)$Å^3$; Z = 2 ; D_c =

† Two coincident methyl carbon resonances.

1.359 g cm^{-3}, F(000) 360.00, T = 293 K, m = 0.102 mm^{-1}. 3056 reflections in the range $2 < q < 25°$ were collected with graphite-monochromated Mo-K_a radiation; of these 2878 were unique (R_{int} = 0.033) and 1488 had I > 3s(I). The strucuture was solved using SIR92[15] and refined with all non-H atoms allowed anisotropic displacement parameters.[16] H atoms are included as riding atoms in idealised positions. The final R and R_w values are 0.068 and 0.055 for 218 variables. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. Selected bond lengths (Å) : N=N, 1.273(6); C(1) – C(6), 1.588(8); C(1) – C(7), 1.518(8); C(6) – C(7), 1.458(8). Interbond angles (°) in the 3-membered ring: at C(1), 55.9(4); at C(6), 59.6(4); at C(7), 64.5(4).

Correct elemental analyses and completely assignable ^1H and ^{13}C NMR spectra were also obtained for compounds **4b** and **6**.

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