Diels-Alder Reactions of 3,6-Diphenyl-1,2,4,5-Tetrazine and 3,6-Di(2-pyridyl)-1,2,4,5-tetrazine with some 1-Morpholinocycloalkenes

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The reactions of 3,6-diphenyl-1,2,4,5-tetrazine **1** and 3,6-di(2-pyridyl)-1,2,4,5-tetrazine **2** with the enamines **3a-d** derived from morpholine and the 5-,6-,7- and 8-membered cyclic ketones have been investigated. A number of pyridazine derivatives **4-7** most of which are new have been reported. Moreover, a novel procedure for the aromatization of pyridazines **5a-d** to the corresponding pyridazine **7b-d** *via* oxidative elimination using hydrogen peroxide is described. The structures of products **4-7** were confirmed by spectral methods and elemental analysis.

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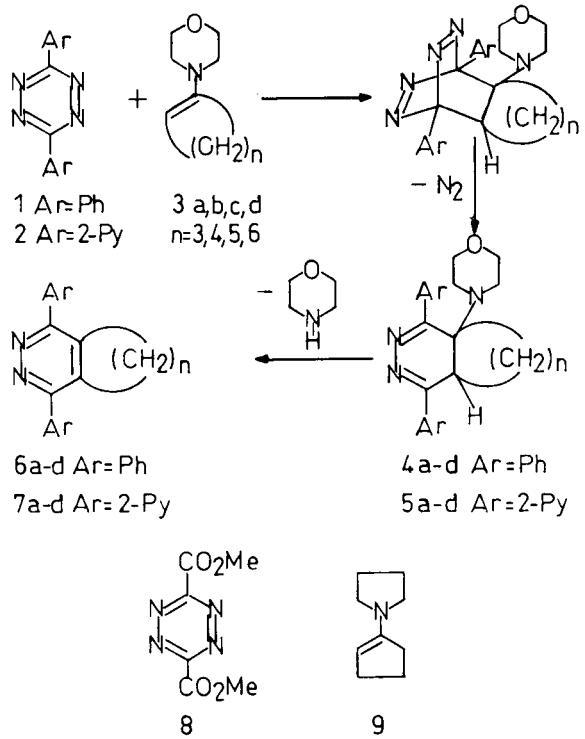
The inverse electron demand Diels-Alder cycloaddition reactions of 3,6-disubstituted-1,2,4,5-tetrazines with alkenes, alkynes, enol ethers and enol esters, ketene acetals, enamines and ynamines to give substituted pyridazines have become well known since the early work of Carboni and Lindsey [1] and Sauer and his coworkers [2]. However, although there are several reports on the reactions of these tetrazines with enamines and heterocyclic enamines [3,4], the reactions of the afore-mentioned tetrazines with enamines derived from cycloalkanones have not been reported. The only exceptions are the reaction of 3,6-diphenyl-1,2,4,5-tetrazine **1** with 1-morpholinocyclopentene **3a** and that of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate **8** with 1-pyrrolidinocyclopentene **9** [2].

Scheme 1



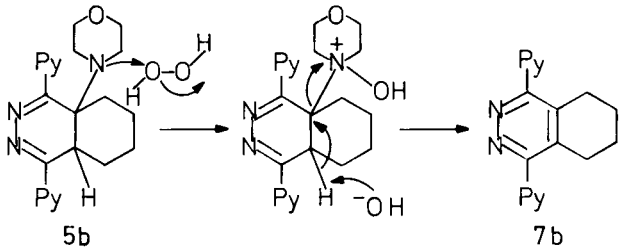
In the present paper, the reactions of the title tetrazines **1** and **2** with the enamines **3a-d** are described. Thus, 3,6-diphenyl-1,2,4,5-tetrazine **1** reacted smoothly with 1-morpholinocyclopentene **3a** in warm acetonitrile, and reacted under reflux with 1-morpholinocyclohexene **3b**, 1-morpholinocycloheptene **3c**, and 1-morpholinocyclooctene **3d** to give the morpholinopyridazines **4a-d** in 88%, 90%, 85% and 48% yield respectively as shown in Scheme 1.

Tetrazines **4a-d** crystallized out of the reaction mixtures as yellow solids. The completion of the reaction was indicated by the discharge of the violet-red color of the starting tetrazine. The order of reactivity was observed to be **3a** > **3c** > **3b** > **3d**. On the other hand, 3,6-di(2-pyridyl)-1,2,4,5-tetrazine **2** was more reactive than tetrazine **1** and reacted readily with enamines **3b-d** in acetonitrile at room temperature to afford the corresponding morpholinopyridazines **5b-d** which came out of the reaction mixtures as yellow crystals in 93%, 96% and 90% yield respectively. The reaction of tetrazine **2** with enamine **3a** in acetonitrile, however, did not lead to the crystallization of the morpholinopyridazine **5a** even after allowing the reaction mixture to stay at room temperature for three days. Rather, upon evaporation of the solvent *in vacuo* and addition of methanol and water to the residue, pyridazine **7a** was obtained as a white solid in 90% yield. The formation of the latter compound **7a** instead of **5a** may be partly attributed to the higher solubility of pyridazine **5a** in acetonitrile compared to that of pyridazine **4a**. Compound **5a** stays in solution long enough for the slow elimination step to take place to produce pyridazine **7a**. Furthermore, refluxing toluene solutions of tetrazine **1** and emanines **3a-d** for periods ranging from 4 hours to 2 days, gave pyridazines **6a-d** in 42-48% yield. The latter compounds could be obtained by refluxing toluene solutions of pyridazine **4a-d** as well. The reaction of tetrazine **1** with enamine **3d** in toluene at reflux temperature to give pyridazine **6d** is superior to the method reported by Haddadin and his coworkers [5] because it gives a higher yield and eliminates the need for chromatography.

The reactions of tetrazine **2** with enamines **3a-d** in refluxing toluene, however, were not clean, and poor yields of pyridazines **7a** and **5b-d** were obtained after 1-3 days of reflux. Obviously, a different method for the preparation of pyridazines **7b-d** was necessary.

It was believed that quaternization of the morpholine moiety in pyridazines **5b-d** would make it a better leaving group and facilitate its elimination to form the required pyridazines **7b-d**. Indeed, the morpholinopyridazines **5b-d** could be converted into their aromatic counterparts **7b-d** by treating methanolic solutions of the former pyridazines **5b-d** with hydrogen peroxide in slight excess at room temperature for 3 days. Pyridazines **7b-d**, white solids, were obtained in 56%, 43% and 82% yields respectively upon diluting the reaction mixtures with water. Unfortunately, this method could not be applied to pyridazines **4a-d** due to their low solubility in methanol at room temperature. A possible mechanism for the conversion of morpholinopyridazines **5b-d** into pyridazines **7b-d** which involves quaternization *via* the electrophilic attack of hydrogen peroxide on the morpholine nitrogen in **5b-d**, is shown in Scheme 2 below.

Scheme 2



The structures of all the products **4-7** were assigned on the basis of their ir and ^{1}H nmr spectra and their correct elemental analyses.

EXPERIMENTAL

Melting points were measured on Electrothermal melting point apparatus and are uncorrected. The ir spectra were recorded as potassium bromide disks using a Pye Unicam SP3-100 spectrophotometer. The ^{1}H nmr spectra were run in deuteriochloroform with tetramethylsilane as internal reference using a Brucker WP 80 SY spectrometer. Enamines **3a-d**, 3,6-diphenyl-1,2,4,5-tetrazine **1** and 3,6-di(2-pyridyl)-1,2,4,5-tetrazine **2** were prepared according to the literature methods [6-8].

General Procedure A: Reactions of 3,6-Diphenyl-1,2,4,5-tetrazine **1** or 3,6-Di(2-pyridyl)-1,2,4,5-tetrazine **2** with Enamines **3a-d**.

Tetrazine **1** or **2** (0.47 g, 2 mmoles) was dissolved in acetonitrile (20 ml) with boiling. The enamine **3a-d** (3-4 mmoles) was then added to the solution. The reaction mixture was allowed to stand at room temperature in all cases except for the reactions of tetrazine **1** with enamines **3b-d** which were run under reflux for 7, 2 and 72 hours respectively. The products **4a-d** and **5b-d** crystallized out upon cooling and were recrystallized from acetonitrile.

General Procedure B: Reactions of 3,6-Diphenyl-1,2,4,5-tetrazine **1** with Enamines **3a-d** in refluxing Toluene.

Tetrazine **1** (0.94 g, 4 mmoles) and enamine **3a-d** (5-6 mmoles) were dissolved in toluene (50 ml) under boiling and reflux was continued for 4-12 hours for enamines **3a-c** and for 2 days for enamine **3d**. Pyridazines **6a-d** were obtained by concentrating the reaction mixtures followed by dilution with hexane and were recrystallized from toluene-hexane or methanol-water mixtures.

General Procedure C: Conversion of Pyridazines **5b-d** into **7b-d**.

Pyridazines **5b-d** (4 mmoles) were dissolved in methanol (10 ml). Hydrogen peroxide (5-6 mmoles) was added to the methanolic solutions and the mixtures were allowed to stay at room temperature for 3 days after which water was added to induce crystallization of the products which were collected and recrystallized from methanol-water.

4a,6,7,7a-Tetrahydro-4a-morpholino-1,4-diphenyl-5*H*-cyclopenta[*d*]pyridazine **4a**.

This compound was obtained in a yield of 88% (0.65 g) mp 182-183° (lit [2] 180°); ir (potassium bromide): 3060, 2960, 2865, 2820, 1590, 1555, 1445, 1370, 1280, 1125, 910, 800, 670 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.42-8.19 (m, 2H), 8.19-7.91 (m, 2H), 7.57-7.33 (m, 6H), 3.78-3.42 (t, 4H), 3.42-3.24 (m, 1H), 2.63-2.39 (t, 4H), 2.39-1.15 (two m, 6H).

4a,5,6,7,8,8a-Hexahydro-4a-morpholino-1,4-diphenylphthalazine **4b**.

This compound was obtained in a yield of 90% (0.70 g) mp 238-240°; ir (potassium bromide): 3060, 2910, 2860, 2820, 1590, 1555, 1490, 1445, 1370, 1275, 1125, 780, 710, 700 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.18-7.80 (m, 4H), 7.59-7.29 (m, 6H), 3.74-3.50 (t, 4H), 3.29-3.00 (m, 1H), 2.79-2.53 (t, 4H), 2.20-0.70 (m, 8H).

Anal. Calcd. for $C_{24}H_{27}N_3O$: C, 77.18; H, 7.29; N, 11.25. Found: C, 77.39; H, 7.16; N, 11.37.

4a,6,7,8,9,9a-Hexahydro-4a-morpholino-1,4-diphenyl-5*H*-cyclohepta[*d*]pyridazine **4c**.

This compound was obtained in a yield of 85% (0.67 g) mp 160-162°; ir (potassium bromide): 3060, 2910, 2860, 1590, 1550, 1490, 1445, 1370, 1225, 1125, 890, 690 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.18-7.82 (m, 4H), 7.64-7.29 (m, 6H), 3.79-3.44 (t, 4H), 3.44-3.15 (m, 1H), 2.79-2.50 (t, 4H), 2.38-1.08 (m, 10H).

Anal. Calcd. for $C_{25}H_{29}N_3O$: C, 77.48; H, 7.54; N, 10.84. Found: C, 77.52; H, 7.60; N, 10.94.

4a,5,6,7,8,9,10,10a-Octahydro-4a-morpholino-1,4-diphenylcycloocta[*d*]pyridazine **4d**.

This compound was obtained in a yield of 48% (0.40 g) mp 185-187°; ir (potassium bromide): 3060, 2910, 2860, 1590, 1555, 1500, 1445, 1370, 1350, 1275, 1130, 1030, 995, 840, 690 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.15-7.34 (three m, 10H), 3.66-3.46 (t, 4H), 3.46-3.30 (m, 1H), 2.80-2.60 (t, 4H), 2.24-1.19 (m, 12H).

Anal. Calcd. for $C_{26}H_{31}N_3O$: C, 77.77; H, 7.78; N, 10.40. Found: C, 77.56; H, 7.70; N, 10.24.

4a,5,6,7,8,8a-Hexahydro-4a-morpholino-1,4-di(2-pyridyl)phthalazine **5b**.

This compound was obtained in a yield of 93% (0.70 g) mp 179-181°; ir (potassium bromide): 3040, 2915, 2910, 2825, 2810, 1560, 1450, 1425, 1360, 1270, 1140, 1115, 1025, 980, 785, 750,

690 cm^{-1}; ^1H nmr (deuteriochlororform): δ 8.76-8.58 (m, 2H), 8.58-8.35 (dm, 1H), 8.20-8.00 (dm, 1H), 7.94-7.65 (m, 2H), 7.44-7.20 (m, 2H), 4.08-3.82 (m, 1H), 3.57-2.56 (t, 4H; m and t, 5H), 1.88-0.95 (m, 6H), 0.95-0.30 (m, 1H).

Anal. Calcd. for $C_{22}H_{25}N_5O$: C, 70.37; H, 6.71; N, 18.65. Found: C, 70.29; H, 6.71; N, 18.59.

4a,6,7,8,9,9a-Hexahydro-4a-morpholino-1,4-di(2-pyridyl)-5*H*-cyclohepta[*d*]pyridazine **5c**.

This compound was obtained in a yield of 96% (0.75 g) mp 179-180°; ir (potassium bromide): 3040, 2900, 2820, 2805, 1585, 1450, 1360, 1350, 1270, 1115, 1010, 790, 750, 695 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.77-8.60 (m, 2H), 8.54-8.37 (dm, 1H), 8.08-7.65 (dm, 1H, m, 2H), 7.46-7.22 (m, 2H), 4.34-4.15 (m, 1H), 3.68-3.30 (m, 4H), 3.14-2.43 (m, 6H), 2.08-1.25 (m, 8H).

Anal. Calcd. for $C_{23}H_{27}N_5O$: C, 70.92; H, 6.99; N, 17.98. Found: C, 71.13; H, 7.06; N, 18.00.

4a,5,6,7,8,9,10,10a-Octahydro-4a-morpholino-1,4-di(2-pyridyl)cycloocta[*d*]pyridazine **5d**.

This compound was obtained in a yield of 90% (0.72 g) mp 171-173°; ir (potassium bromide): 3050, 2960, 2900, 2860, 2800, 1580, 1460, 1350, 1270, 1140, 1035, 990, 925, 750, 725, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.75-8.55 (m, 2H), 8.55-8.36 (dm, 1H), 7.97-7.64 (m, 3H), 7.42-7.20 (m, 2H), 4.45-4.30 (m, 1H), 3.54-3.24 (m, 4H), 3.09-2.64 (m, 4H), 2.64-1.15 (m, 12H).

Anal. Calcd. for $C_{24}H_{29}N_5O$: C, 74.19; H, 7.52; N, 18.03. Found: C, 74.12; H, 7.39; N, 17.94.

6,7-Dihydro-1,4-diphenyl-5*H*-cyclopenta[*d*]pyridazine **6a**.

Compound **6a** was obtained in a yield of 49% (0.53 g) mp 161-163° (lit [5] 158-159°); ir (potassium bromide): 3050, 2960, 2900, 2860, 1540, 1480, 1440, 1370, 1065, 1010, 910, 760, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.00-7.80 (m, 4H), 7.60-7.42 (m, 6H), 3.33-3.08 (t, 4H), 2.33-1.90 (quint, 2H).

5,6,7,8-Tetrahydro-1,4-diphenylphthalazine **6b**.

Compound **6b** was obtained in a yield of 48% (0.55 g) mp 172-174° (lit [5] 171-173°); ir (potassium bromide): 3040, 2920, 2860, 1540, 1435, 1410, 1370, 1325, 1065, 765, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.70-7.27 (m, 10H), 2.90-2.54 (quint, 4H), 2.00-1.57 (quint, 4H).

6,7,8,9-Tetrahydro-1,4-diphenyl-5*H*-cyclohepta[*d*]pyridazine **6c**.

Compound **6c** was obtained in a yield of 42% (0.50 g) mp 152-154° (lit [5] 150-152°); ir (potassium bromide): 3040, 3000, 2980, 2910, 2840, 1540, 1500, 1490, 1435, 1375, 1070, 1020, 760, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.70-7.35 (m, 10H), 3.00-2.73 (m, 4H), 2.05-1.49 (m, 6H).

5,6,7,8,9,10-Hexahydro-1,4-diphenylcycloocta[*d*]pyridazine **6d**.

Compound **6d** was obtained in a yield of 47% (0.59 g) mp 163-165° (lit [5] 138-139°); ir (potassium bromide): 3040, 3020, 2910, 2850, 1540, 1470, 1430, 1375, 1175, 1070, 1010, 920, 885, 770, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.68-7.35 (m, 10H), 3.00-2.65 (m, 4H), 1.81-1.22 (m, 8H).

6,7-Dihydro-1,4-di(2-pyridyl)-5*H*-cyclopenta[*d*]pyridazine **7a**.

Compound **7a** was obtained in a yield of 91% (0.50 g) mp 159-161°; ir (potassium bromide): 3020, 2960, 2860, 1580, 1570, 1460, 1440, 1370, 1250, 1150, 1105, 990, 790, 740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.86-8.52 (m, 4H), 8.04-7.71 (m, 2H), 7.48-7.24 (m, 2H), 3.71-3.41 (t, 4H), 2.42-1.91 (quint, 2H).

Anal. Calcd. for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.43. Found: C, 74.54; H, 5.08; N, 20.38.

5,6,7,8-Tetrahydro-1,4-di(2-pyridyl)phthalazine **7b**.

Compound **7b** was obtained in a yield of 57% (0.48 g) mp 117-119°; ir (potassium bromide): 3040, 3000, 2910, 2850, 1580, 1560, 1550, 1470, 1420, 1410, 1380, 1220, 1150, 1140, 1110, 990, 800, 760, 750, 730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.86-8.58 (m, 2H), 8.10-7.72 (m, 4H), 7.49-7.23 (m, 2H), 3.22-2.81 (quint, 4H), 2.00-1.58 (quint, 4H).

Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.06; H, 5.60; N, 19.37.

6,7,8,9-Tetrahydro-1,4-di(2-pyridyl)-5*H*-cyclohepta[*d*]pyridazine **7c**.

Compound **7c** was obtained in a yield of 42% (0.5 g) mp 129-130°; ir (potassium bromide): 3025, 3010, 2920, 2850, 1585, 1565, 1460, 1380, 1115, 1000, 785, 765 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.90-8.66 (m, 2H), 8.06-7.80 (m, 4H), 7.49-7.23 (m, 2H), 3.20-2.90 (m, 4H), 2.08-1.46 (m, 6H).

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53. Found: C, 75.52; H, 6.17; N, 18.55.

5,6,7,8,9,10-Hexahydro-1,4-di(2-pyridyl)cycloocta[*d*]pyridazine **7d**.

Compound **7d** was obtained in a yield of 80% (1.0 g) mp 161-163°; ir (potassium bromide): 3100, 3060, 1550, 1490, 1220, 1100, 900, 860 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.87-8.55 (m, 2H), 8.07-7.68 (m, 4H), 7.52-7.16 (m, 2H), 3.29-2.84 (t, 4H), 2.00-1.13 (two m, 8H).

Anal. Calcd. for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.70. Found: C, 75.74; H, 6.39; N, 17.69.

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