A SIMPLE AND EFFICIENT ROUTE TO CYCLOALKENE-FUSED 2,3-DIHYDROPHTHALAZINE-1(4*H*),4-DIONES

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Abstract – A convenient method for the preparation of cycloalkene-annelated 2,3-dihydrophthalazine-1(4*H*),4-diones, starting from a pyridazino[4,5-*d*]pyridazine diazadiene is detailed.

2,3-Dihydrophthalazine-1(4*H*),4-diones ("phthalylhydrazides") are commonly used intermediates in the synthesis of drug molecules with a 1,4-disubstituted phthalazine substructure, such as the antihypertensive agent *dihydralazine* (1,4-dihydrazinophthalazine).[1] Moreover, these compounds have attracted considerable attention because they can be easily oxidized to phthalazine-1(4*H*),4-diones. The latter diones exhibit interesting chemiluminescence phenomena,[2] they have pronounced (diaza)dienophilic properties,[3] and - moreover - they can be used as precursors for the preparation of benzocyclobutene-1,2-diones[4] which, in turn, represent useful synthons. Phthalylhydrazides are usually obtained by condensation of appropriate phthalic acid derivatives like esters or anhydrides with hydrazine,[5] thus this access is limited by the availability of the corresponding dicarboxylic acids.

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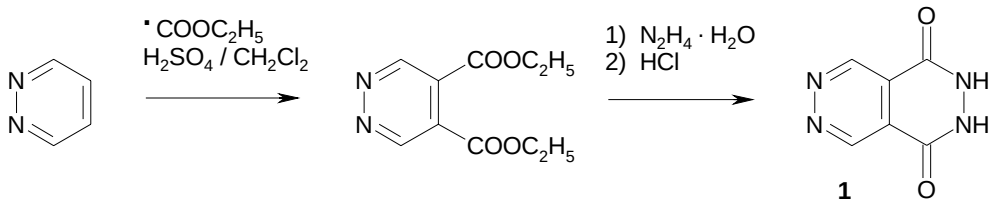
As a complementary synthetic pathway to 2,3-dihydrophthalazine-1(4*H*),4-diones, we now elaborated a method which is based on an inverse-electron-demand Diels-Alder reaction[6] of a pyridazino[4,5-*d*]pyridazine derivative as the key step. This sequence permits the preparation of simple, but so far unknown phthalylhydrazides with a cycloalkene ring of variable size fused to the [*g*] edge of the phthalazine skeleton, which are of interest e.g. as building blocks for the synthesis of potential antihypertensive agents. Depending on the number of methylene units in the cycloalkene "handle" of such compounds, the steric and lipophilic properties of the target structures can be gradually varied, which should provide some insight into structure-activity relationships.

In view of the known ability of pyridazino[4,5-*d*]pyridazine derivatives to undergo "inverse" Diels-Alder reactions with electron-rich dienophiles,[7-9] the dione **1**[10] was considered a sufficiently reactive diazadiene in combination with various cyclic enamines as dienophilic reagents. Compound **1** can be prepared most conveniently in two steps from pyridazine, employing the radicalic ethoxy-carbonylation procedure reported by Heinisch and Lötsch,[11] followed by cyclization of the crude diester thus obtained with hydrazine.

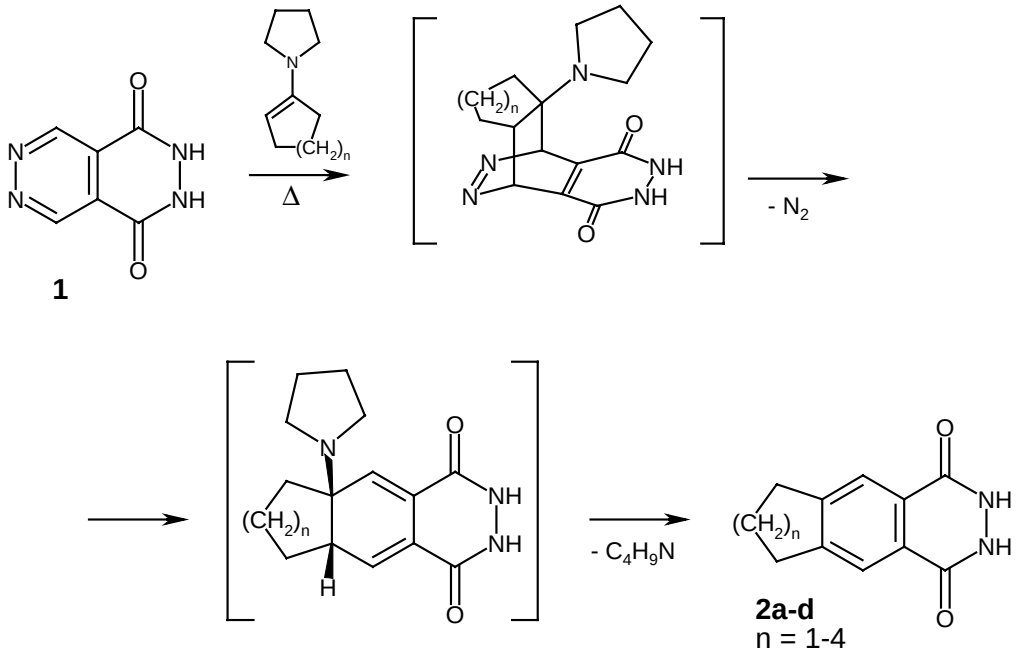
Scheme 1.



First experiments employing boiling dioxane as the solvent showed that at this temperature (101°C) only very reactive enamines like 1-pyrrolidino-1-cyclopentene effect the desired cycloaddition with **1** at a sufficient conversion rate. However, when the reaction is carried out in the same solvent at 180°C, using an autoclave, also six- and eight-membered enamines (which are known to

be less reactive[12-14]) can be successfully employed. The reaction mechanism involves formation of a highly strained cycloadduct which immediately loses molecular nitrogen, followed by spontaneous elimination of pyrrolidine, thus leading to aromatic products of type **2** in all cases.

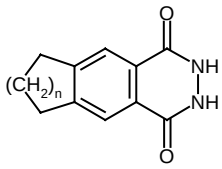
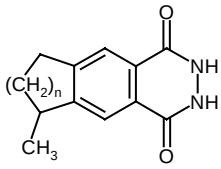
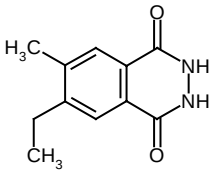
Scheme 2.



Employment of enamines derived from 2-substituted cyclic ketones (2-methylcyclopentanone, 2-methylcyclohexanone) permits the preparation of the corresponding 6-substituted cycloalka[*g*]phthalazine derivatives (compounds **3**) despite the increased steric hindrance of the dienophilic substructure in such reagents. Whereas an attempted reaction of **1** with *N*-styrylmorpholine gave no defined product, employment of another open-chain enamine, 3-pyrrolidino-2-pentene, under the conditions described above smoothly afforded the 6,7-disubstituted 2,3-dihydrophthalazine-1(4*H*),4-dione **4**.

In conclusion, the new method provides an easy and convenient route to various hitherto inaccessible 2,3-dihydrophthalazine-1(4*H*),4-dione derivatives in only three steps from commercially available material. Yields and reaction times for compounds **2a-d**, **3a,b**, and **4** are summarized below.

Table.

							
n	1	2	3	4	1	2	-
Compd.	**2a**	**2b**	**2c**	**2d**	**3a**	**3b**	**4**
Reaction time	24 h	48 h	24 h	24 h	24 h	48 h	24 h
Yield	69%	44%	76%	54%	60%	36%	53%

Experimental

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded for potassium bromide pellets on a Perkin-Elmer 1605 FT-IR spectrophotometer. The ^{1}H-NMR spectra were obtained on a Varian Unity*plus* 300 (300 MHz) spectrometer, using deuteriodimethyl-sulfoxide as solvent. Elemental analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna. The following enamines were prepared according to the method described in lit.[15]: 1-pyrrolidino-1-cyclopentene, 1-pyrrolidino-1-cyclohexene, 1-pyrrolidino-1-cycloheptene, 1-pyrrolidino-1-cyclooctene, 5-methyl-1-pyrrolidino-1-cyclopentene, 6-methyl-1-pyrrolidino-1-cyclohexene; the pyrrolidino enamine derived from 3-pentanone was obtained following the procedure given in lit.[16].

2,3-Dihydropyridazino[4,5-*d*]pyridazine-1(4*H*),4-dione[10] (**1**) (modification of the two separate steps reported previously[10,11]).

Following the procedure described in lit.,[11] 3.4 g (0.03 mol) of hydrogen peroxide (30%) were added dropwise at -10° - 0°C to 5.2 g (0.045 mol) of ethyl pyruvate with stirring. The viscous liquid was kept at the same temperature for 15 min, then it was added dropwise to a vigorously stirred mixture of pyridazine (0.8 g, 0.01 mol), water (4 ml), concentrated sulfuric acid (3.0 g, 0.03 mol), $FeSO_4 \cdot 7\ H_2O$ (6.8 g, 0.03 mol), and CH_2Cl_2 (30 ml) at -5°C - 0°C. Stirring was continued for another 15 min, then the mixture was poured into ice-water and it was extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated. Excess ethyl pyruvate was removed by Kugelrohr distillation at 10 mbar/80°C. The crude diethyl 4,5-pyridazinedicarboxylate thus obtained was dissolved in 15 ml of ethanol. After addition of 1.0 g (0.02 mol) of hydrazine hydrate (100%), the mixture was refluxed for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in water (20 ml). The solution was acidified by addition of 2*N* HCl, and the resulting precipitate was collected by filtration, washed with water, and dried to give 1.0 g (61%, related to pyridazine) of the dione **1**, mp > 340°C (lit.[10] mp > 340°C).

General Procedure for the Preparation of the Phthalylhydrazides **2a-d**, **3a,b**, and **4**.

To a suspension of 164 mg (1 mmol) of compound **1** in 10 ml of 1,4-dioxane was added the appropriate enamine (4 mmol), and the mixture was heated in a teflon-lined autoclave to 180°C for 24 hours (for compounds **2a**, **2c**, **2d**, **3a**, and **4**) or 48 hours (for compounds **2b** and **3b**), respectively. The volatile components were removed under reduced pressure (using a rotary evaporator and then a Kugelrohr distillation apparatus). The residue was taken up in water (15 ml) and was made strongly alkaline by addition of 2*N* NaOH. After addition of charcoal, the solution was stirred for 15 min at room temperature, then it was filtered and acidified with 6*N* H_2SO_4. The precipitate was collected by filtration, washed with water, and

dried. Analytical samples were obtained by recrystallization from dimethyl-formamide/water and/or by sublimation at 200°C/10^{-1} mbar.

2,3,7,8-Tetrahydro-1*H*-cyclopenta[*g*]phthalazine-1,4(6*H*)-dione (**2a**).

This compound was obtained from **1** and 1-pyrrolidino-1-cyclopentene as almost colorless crystals, mp 310°C (decomp.). Yield: 140 mg (69%). *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.01; H, 5.19; N, 13.61. IR: 3158, 3013, 1634, 1592, 1555, 1450, 1354, 1250, 1167, 1067, 811 cm^{-1}. ^{1}H-NMR: δ 11.30 (br, 2H, NH), 7.87 (s, 2H, Ar-H), 3.04-2.99 (m, 4H, Ar-CH_2), 2.12-2.02 (m, 2H, CH_2).

2,3,6,7,8,9-Hexahydrobenzo[*g*]phthalazine-1(4*H*),4-dione (**2b**).

This compound was obtained from **1** and 1-pyrrolidino-1-cyclohexene as almost colorless crystals, mp > 335°C (decomp.). Yield: 96 mg (44%). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.94; H, 5.72; N, 13.10. IR: 2929, 1654, 1602, 1496, 1326, 818 cm^{-1}. ^{1}H-NMR: δ 11.30 (br, 2H, NH), 7.73 (s, 2H, Ar-H), 2.94-2.85 (m, 4H, Ar-CH_2), 1.82-1.72 (m, 4H, CH_2).

2,3,7,8,9,10-Hexahydro-1*H*-cyclohepta[*g*]phthalazine-1,4(6*H*)-dione (**2c**).

This compound was obtained from **1** and 1-pyrrolidino-1-cycloheptene as light brown crystals, mp 345°C (decomp.). Yield: 175 mg (76%). *Anal.* Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.57; H, 6.34; N, 12.42. IR: 3151, 2926, 1643, 1590, 1454, 1342, 1269, 1188, 1081, 811 cm^{-1}. ^{1}H-NMR: δ 11.80-10.80 (br, 2H, NH), 7.77 (s, 2H, Ar-H), 2.97-2.87 (m, 4H, Ar-CH_2), 1.81-1.79 (m, 2H, CH_2), 1.61-1.59 (m, 4H, CH_2).

2,3,6,7,8,9,10,11-Octahydrocycloocta[*g*]phthalazine-1(4*H*),4-dione (**2d**).

This compound was obtained from **1** and 1-pyrrolidino-1-cyclooctene as almost colorless crystals, mp > 300°C (decomp.). Yield: 133 mg (54%). *Anal.* Calcd. for $C_{14}H_{16}N_2O_2 \cdot 0.15\ H_2O$: C, 68.08; H, 6.65; N, 11.34. Found: C, 68.10; H, 6.61; N,

11.46. IR: 3155, 3018, 1640, 1590, 1453, 1262, 808 cm^{-1}. ^{1}H-NMR: δ 11.80-10.80 (br, 2H, NH), 7.79 (s, 2H, Ar-H), 2.93-2.89 (m, 4H, Ar-CH_2), 1.73-1.60 (m, 4H, CH_2), 1.42-1.25 (m, 4H, CH_2).

2,3,7,8-Tetrahydro-6-methyl-1*H*-cyclopenta[*g*]phthalazine-1,4(6*H*)-dione (**3a**).

This compound was obtained from **1** and 5-methyl-1-pyrrolidino-1-cyclopentene as colorless crystals, mp > 305°C (decomp.). Yield: 129 mg (60%). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.54; H, 5.70; N, 12.84. IR: 3153 , 2964, 1639, 1593, 1455, 1354, 1235, 1164, 1069, 811 cm^{-1}. ^{1}H-NMR (d_6-DMSO/$CDCl_3$): δ 7.84 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 3.30-3.10 (m, 1H, Ar-CH), 3.10-2.80 (m, 2H, Ar-CH_2), 2.40-2.20 and 1.70-1.50 (m, 2H, CH_2), 1.28 (d, J = 6.6 Hz, 3H, CH_3).

2,3,6,7,8,9-Hexahydro-6-methylbenzo[*g*]phthalazine-1(4*H*),4-dione (**3b**).

This compound was obtained from **1** and 6-methyl-1-pyrrolidino-1-cyclohexene as colorless crystals, mp 280°C (decomp.). Yield: 82 mg (36%). *Anal.* Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.11; H, 6.05; N, 12.15. IR: 3163, 2929, 1646, 1600, 1456, 1324, 1260, 1081, 912, 809 cm^{-1}. ^{1}H-NMR: δ 11.30 (br, 2H, NH), 7.87 (s, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 3.10-3.00 (m, 1H, Ar-CH), 3.00-2.90 (m, 2H, Ar-CH_2), 2.00-1.40 (m, 4H, CH_2), 1.30 (d, J = 6.9 Hz, 3H, CH_3).

2,3-Dihydro-6-ethyl-7-methylphthalazine-1(4*H*),4-dione (**4**).

This compound was obtained from **1** and 3-pyrrolidino-2-pentene as colorless crystals, mp > 300°C (decomp.). Yield: 109 mg (53%). *Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.42; H, 6.22; N, 13.63. IR: 3162, 2912, 1657, 1623, 1490, 1354, 1243, 1189, 1094, 818 cm^{-1}. ^{1}H-NMR: δ 11.40 (br, 2H, NH), 7.81 (s, 2H, Ar-H), 2.76 (q, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 2.44 (s, 3H, Ar-CH_3), 1.22 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$).

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