Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5919–5926

TETRAHEDRON

Synthesis of the dibenzo[f,h]phthalazine and dibenzo[f,h]cinnoline skeleton via a 'Suzuki–Pd-catalyzed intramolecular arylation' and a 'Suzuki–Pschorr' approach

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Received 7 April 2003; revised 8 May 2003; accepted 5 June 2003

Cordially dedicated to Professor László Tőke on the occasion of his 70th birthday.

Abstract—Palladium-catalyzed intramolecular arylation of 2-benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one yielded hitherto unknown 2-benzyldibenzo[f,h]phthalazin-1(2*H*)-one. The synthesis of this new tetracyclic pyridazinone from 2-benzyl-5-(2-aminophenyl)-4-phenylpyridazin-3(2*H*)-one via a Pschorr type reaction was also investigated. Similarly, the construction of 2-methyldibenzo[f,h]cinnolin-3(2*H*)-one from 2-methyl-5-(2-bromophenyl)-6-phenylpyridazin-3(2*H*)-one and 2-methyl-5-(2-aminophenyl)-6-phenylpyridazin-3(2*H*)-one is also reported. Removal of the *N*-benzyl protective group of 2-benzyl-dibenzo[f,h]phthalazin-1(2*H*)-one with $AlCl_3$ yielded unsubstituted dibenzo[f,h]phthalazin-1(2*H*)-one.

1. Introduction

Recently, our laboratories focused on the synthesis of polycyclic pyridazinones via a new approach starting from easily accessible 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones. This new strategy consists of a Suzuki arylation of a chloropyridazin-3(2*H*)-one with a properly *ortho* substituted arylboronic acid, followed by a ring closure step (implying a S_N reaction, lactonization, electrophilic attack of a nitrene, etc.).[1–3] In the frame of this project we investigated Suzuki arylation on 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones.[1a–c] However, a selective reaction could not be performed since a mixture of regioisomeric monoarylated and the diarylated pyridazinones is formed; the relative ratio depends on the arylboronic acid used. To avoid this selectivity problem we have developed an efficient procedure based on the application of 'provisionally masked functionalities' (PMF). The requirements for a PMF could be formulated as follows: (i) it should be easily and selectively introducible in the 4 or 5 position of the 4,5-dichloropyridazin-3(2*H*)-one, (ii) it should be inert in the Suzuki arylation of the chloropyridazin-3(2*H*)-one and (iii) after the Suzuki arylation it should be available, as such or modified, for further substitution or ring closure reactions.

Recently, we reported the use of a methoxy group as a PMF for the synthesis of pyridazino[4,5-*c*]isoquinolinones and isochromeno[3,4-*d*]pyridazinediones.[1c,j] This group meets the above mentioned requirements since we[1a,c] and others[4–6] found that either of the chlorine substituents of 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones can be selectively replaced by a methoxy group. Besides, the methoxy group of 4-aryl-5-methoxypyridazin-3(2*H*)-ones can be transformed into a triflate[1j] which is a good leaving group for palladium-catalyzed reactions. Via Suzuki arylation on these triflates, we obtained 4,5-diarylpyridazin-3(2*H*)-ones with two differently substituted phenyl groups, without selectivity problems.

As a continuation of this research we now report on new approaches towards the synthesis of two 1,2-diazine analogues of triphenylene, dibenzo[f,h]phthalazin-1(2*H*)-one and dibenzo[f,h]cinnolin-3(2*H*)-one, starting from 4,5- and 5,6-diarylpyridazin-3(2*H*)-ones respectively via a palladium-catalyzed intramolecular arylation[7,8] as well as via a Pschorr[9,10] type reaction. The dibenzo[f,h]cinnolin-3(2*H*)-one skeleton has already been prepared by an entirely different route;[11] the dibenzo[f,h]phthalazin-1(2*H*)-one

Keywords: intramolecular arylation; palladium; Suzuki reaction; Pschorr reaction; pyridazinone.
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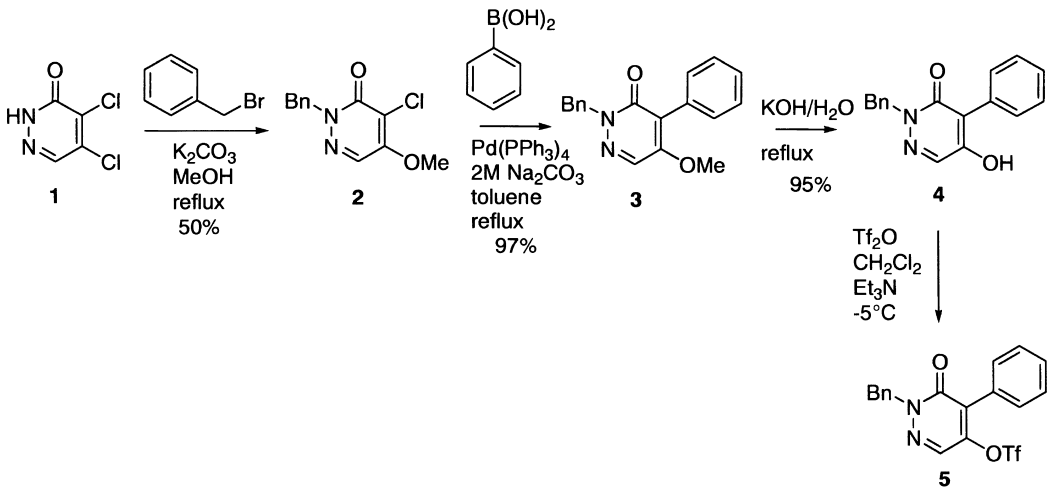
doi:10.1016/S0040-4020(03)00953-0

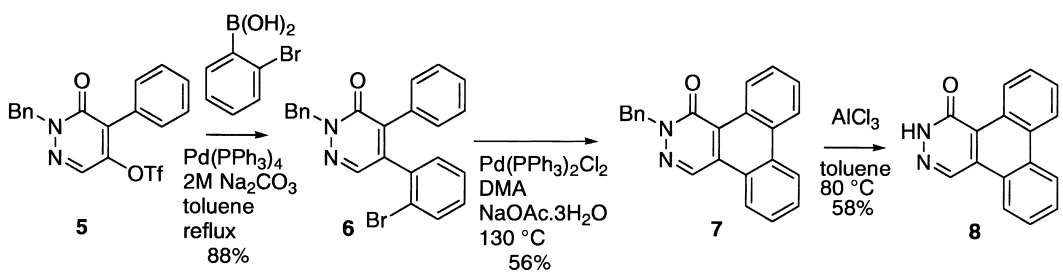
skeleton however is hitherto unknown. Phenylated dibenzo[f,h]cinnoline and dibenzo[f,h]phthalazine have only been reported in a photocyclization study on 3,4,6-triphenyl- and 3,4,5,6-tetraphenylpyridazines.[12]

2. Results and discussion

First we focused on the construction of the dibenzo[f,h]phthalazin-1(2*H*)-one and dibenzo[f,h]cinnolin-3(2*H*)-one skeleton using a palladium-catalyzed intramolecular arylation (Scheme 2).[7,8] 2-Benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one (**6**) was prepared from 2-benzyl-4-phenyl-5-trifluoromethanesulfonyloxypyridazin-3(2*H*)-one (**5**) via a Suzuki arylation with 2-bromophenylboronic acid under the same conditions as previously reported by us for similar reactions.[1j] The starting material for the Suzuki reaction (**5**) was obtained from 4,5-dichloropyridazin-3(2*H*)-one (**1**) using a reaction sequence (Scheme 1) developed earlier in our laboratories:[1a,j] benzylation and methoxylation in a one-pot reaction (**2**), Suzuki reaction (**3**), alkaline hydrolysis (**4**) and subsequent triflate formation (**5**). Cyclodehydrohalogenation of **6** could be realized in DMA at 130°C with $Pd(PPh_3)_2Cl_2$ precatalyst as Pd(0) source and NaOAc as base (Scheme 2). Disappointingly, the intramolecular palladium-catalyzed reaction was rather slow. After 16 h only 30% of 2-benzyldibenzo-[f,h]phthalazin-1(2*H*)-one (**7**) was obtained as well as 39% recovery of the starting material (**6**). Attempts to add lithium halogenide salts to speed up the cyclization reaction were unsuccessful and even slower reactions were obtained (Table 1).[13] Addition of LiCl or LiI yielded less than 10% of **7** and higher recoveries of starting material in comparison with the reference experiment. Finally, a higher yield (56%) of **7** could be obtained by prolonging the reaction time from 16 to 64 h (Table 1). In this case 10% of starting material remained in the reaction mixture. Deprotection of **7** with $AlCl_3$ smoothly gave unsubstituted dibenzo[f,h]phthalazin-1(2*H*)-one (**8**) in good yield (Scheme 2).[14] Under similar reaction conditions as for the synthesis of **7** we studied the cyclodehydrohalogenation of 2-methyl-5-(2-bromophenyl)-6-phenylpyridazin-3(2*H*)-one (**13**) (Scheme 3). In this case, the cyclization reaction was considerably faster since no **13** remained after 8 h of heating. The desired 2-methyldibenzo[f,h]cinnolin-3(2*H*)-one (**14**) could be isolated in 46% yield after column chromatography and subsequent recrystallization. The substrate for palladium-catalyzed cyclodehydrobromination (**13**) was obtained from 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one (**12**) via Suzuki arylation with 2-bromophenylboronic acid under Gronowitz conditions as previously reported by us for related Suzuki arylations with ortho substituted arylboronic acids on this substrate[1d,15] (Scheme 3). Interestingly, the C–Cl bond of **12** seems to be more reactive towards oxidative addition than the C–Br bond of 2-bromophenylboronic acid in the studied Suzuki reaction. In principal, based on the oxidative addition rate of aryl halogenides to $Pd(PPh_3)_2$ catalyst, one could expect that 2-bromophenylboronic acid would preferentially react with itself, consuming all the boronic acid, yielding only undesired coupling products. The preferential reaction of the C–Cl bond of **12** can be explained by taking into account that the studied carbon chlorine bond is part of a vinylogous carbamoyl chloride which dramatically increases its reactivity

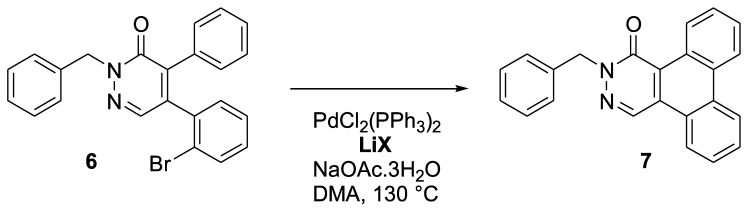


Scheme 1.



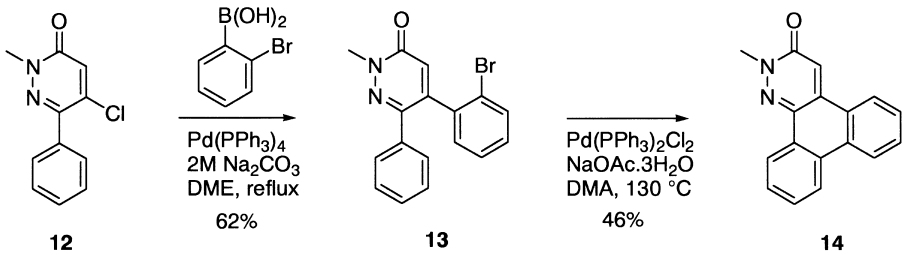
Scheme 2.

Table 1. Effect of lithium halogenide salts on the cyclodehydrohalogenation of **6**



Additive[a]	**7** (%)	**6** (%)	Reaction time (h)
–	30	39	16
–	56	10	64
LiCl	7	63	16
LiI	4	90	16

Reaction conditions: **6**, $Pd(PPh_3)_2Cl_2$ (0.2 equiv.), $NaOAc.3H_2O$ (2 equiv.), DMA, 130°C.
[a] 3 equiv. of LiX were added.

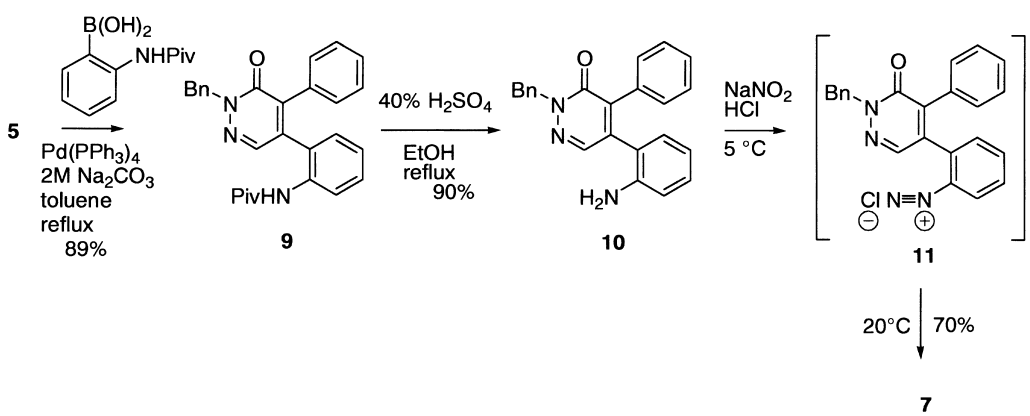


Scheme 3.

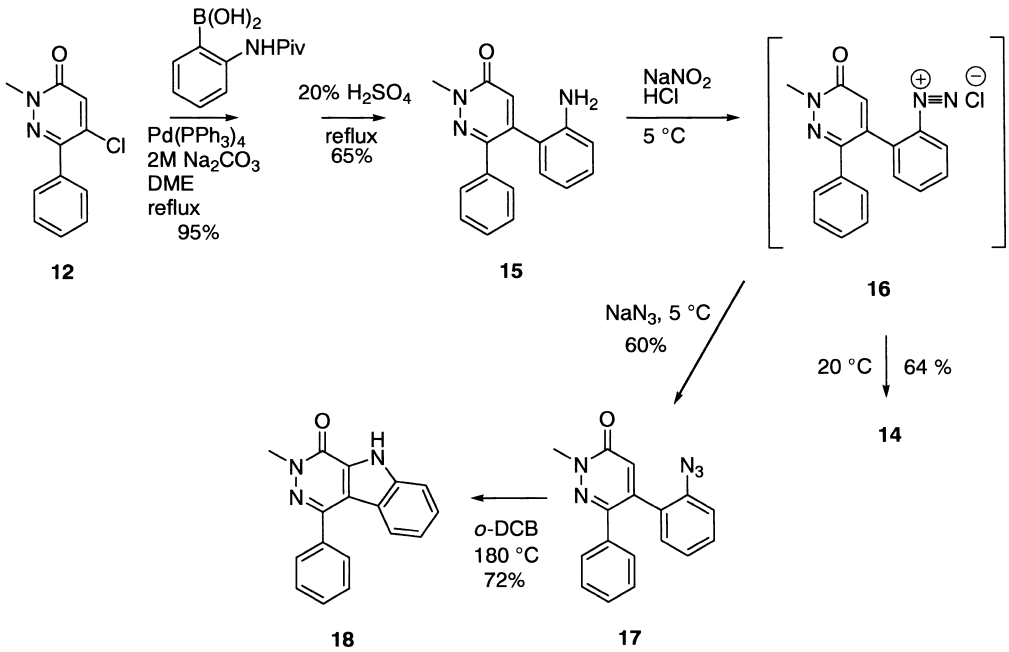
for oxidative addition to $Pd(PPh_3)_2$ in comparison with unactivated C–Cl bonds.[16]

The moderate results obtained for the palladium-catalyzed intramolecular arylation of **6** prompted us to search for an alternative approach to construct 1,2-diazine analogues of triphenylene (Schemes 4 and 5). Recently, we studied the synthesis of 3-methyl-1-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-b]indol-4-one (**18**) making use of the thermal cyclization reaction of 5-(2-azidophenyl)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**17**) involving the formation of a nitrene (Scheme 5).[1d] The required azide was prepared from the corresponding diazonium salt (**16**) by substitution with NaN_3. In the present study the reaction mixture containing **16** was simply allowed to reach room temperature instead of adding NaN_3 and further stirring at 0–5°C. Now decomposition of the diazonium salt occurred, followed by intramolecular arylation (Scheme 5), and **14** could be obtained in a higher overall yield (40% from **12**) than with the palladium-catalyzed ring closure approach (29% from **12**). Interestingly, the combination of a Suzuki arylation reaction with a protected 2-aminophenylboronic acid such as 2-pivaloylaminophenylboronic acid followed by deprotection, diazotization and in situ Pschorr type ring closure has never been reported yet.[9,10]

Analogously, **7** was prepared from 5-(2-aminophenyl)-2-benzyl-4-phenylpyridazin-3(2*H*)-one (**10**) via a Pschorr type ring closure (Scheme 4). Compound **10** was synthesized by Suzuki arylation of **5** with 2-(pivaloylamino)-phenylboronic acid under the same conditions as used for the preparation of **6** followed by deprotection of the



Scheme 4.



Scheme 5.

N-pivaloyl group with strong acid.[17] Due to solubility problems of 2-benzyl-4-phenyl-5-(2-pivaloylaminophenyl)-pyridazin-3(2*H*)-one (**9**) in aqueous sulphuric acid, ethanol was used as a co-solvent for the amide hydrolysis. In this way **10** could be obtained in excellent yield (90%). The diazotization/Pschorr type ring closure of **10** is clearly a superior method for the preparation of **7** since a 70% yield (56% overall yield from **5**) was obtained in only 3 h reaction time in comparison with 56% (49% overall yield from **5**) after 64 h for the intramolecular Pd-catalyzed arylation.

In conclusion, we have studied the synthesis of dibenzo[f,h]phthalazin-1(2*H*)-one and dibenzo[f,h]cinnolin-3(2*H*)-one via a 'Suzuki–Intramolecular Pd-catalyzed arylation' and a 'Suzuki–Pschorr' approach. The latter combination to build up phenanthrene units is unprecedented and looks very attractive as a general tool for the efficient synthesis of phenanthrene containing polycyclic aromatic hydrocarbons and their aza-analogues.[18]

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Unity 400 spectrometer with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. The numbering used for the assignment of NMR-signals is as follows: pyridazinone ring simple figures, 4-substituents (or 6-substituents) primed figures, 5-substituents double primed figures and N-substituents triple primed figures. ^{1}H- and ^{13}C NMR assignments of compounds **7** and **14** are based on 2D NMR techniques. For mass-spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min CH_3OH (0.1% formic acid), using a CapLC HPLC system (Waters, Millford). Product ion spectra and accurate mass data were acquired on a quadrupole-time-of-flight mass spectrometer (QTofII, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (35 V) and capillary voltage (3.3 kV) were optimized on one compound and used for all others. For the determination of the high-resolution *m/z*-values of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated mass of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions was used as a lock mass for the measurement of the accurate mass values of the samples. For the product ion experiments the mass of the $[M+H]^+$ was used as lock mass for the fragments. Fragmentation was induced by low energy collisional activation using different collision energies between 20 and 30 eV. IR spectra were recorded on a Bruker Vector 22 spectrometer. Starting compounds were synthesized by literature procedures: 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[19] (**12**) and 2-pivaloylaminophenylboronic acid,[20] or were purchased from commercial sources: 4,5-dichloropyridazin-3(2*H*)-one (**1**) (Aldrich), benzyl bromide (Acros), phenylboronic acid (Aldrich), 2-bromophenylboronic acid (Aldrich), trifluoromethanesulfonic anhydride (Acros, Aldrich), $Pd(PPh_3)_4$ (Acros) and $PdCl_2(PPh_3)_2$ (Fluka). The synthesis of 3-methyl-1-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one (**18**) from **12** has been published earlier by our laboratories.[1d] Flash column chromatography was performed on Kieselgel 60 (Merck), 0.040–0.063 mm.

3.1.1. 2-Benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one (2). A mixture of 4,5-dichloropyridazin-3(2*H*)-one (**1**) (1.65 g, 10 mmol), potassium carbonate (2.79 g, 20.2 mmol) and benzyl bromide (1.20 mL, 10.1 mmol) in

methanol (55 mL) (distilled from magnesium) was stirred and heated under reflux for 8 h (the reflux condenser was equipped with a drying tube). After cooling down the reaction mixture, the solvent was evaporated under reduced pressure and water was added (100 mL). Subsequently, the water phase was extracted with CH_2Cl_2 (3×100 mL), dried on $MgSO_4$, evaporated to dryness and subjected to flash column chromatography on silica gel with CH_2Cl_2 as the eluent to yield the title compound as white crystals (1.25 g, 50%). The characterization data were identical with those previously reported by us for the preparation of **2** from 2-benzyl-4,5-dichloropyridazin-3(2*H*)-one.[1c]

3.2. General procedure for the synthesis of 2-benzyl-5-methoxy-4-phenylpyridazin-3(2*H*)-one (3), 2-benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one (6) and *N*-[2-(2-benzyl-3-oxo-4-phenyl-2,3-dihydropyridazin-5-yl)phenyl]pivalamide (9) via Suzuki arylation

A mixture of compound **2** or **5** (**3**: 500 mg, 2 mmol; **6**: 670 mg, 1.63 mmol; **9**: 1.086 g, 2.65 mmol), arylboronic acid (**3**: 366 mg, 3 mmol; **6**: 490 mg, 2.44 mmol; **9**: 704 mg, 3.97 mmol) and toluene (**3**: 12 mL; **6**: 10 mL; **9**: 20 mL) was flushed with N_2 for 5 min under magnetic stirring followed by the addition of $Pd(PPh_3)_4$ (**3**: 70 mg, 0.06 mmol; **6**: 60 mg, 0.05 mmol; **9**: 160 mg, 1.14 mmol) and aqueous Na_2CO_3 (2 M, **3**: 2.2 mL; **6**: 1.8 mL; **9**: 2.90 mL) under a stream of N_2 gas. The reaction mixture was stirred and refluxed in an oil bath (temperature of oil bath: 120°C) under a N_2 atmosphere (**3**: 6 h; **6**, **9**: 3 h). After cooling, the solvent was evaporated to dryness under reduced pressure. Ethyl acetate (**3**, **6**: 50 mL; **9**: 80 mL) was added and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered through Celite, washed thoroughly with ethyl acetate (200 mL) and the filtrate was subsequently evaporated to dryness. For the synthesis of **9** an extra washing with CH_2Cl_2 (500 mL) was performed.

3.2.1. 2-Benzyl-5-methoxy-4-phenylpyridazin-3(2*H*)-one (3). The residue was purified by flash column chromatography on silica gel with a mixture of ethyl acetate and hexane (2:8) as the eluent to yield the title compound as white crystals (566 mg, 97%); mp 107–108°C; ν_{max} (KBr): 3058, 3035, 3004, 2952, 1624, 1601, 1494, 1446, 1406, 1352, 1333, 1313, 1268, 1155, 1065, 972, 782, 750, 736, 696, 591, 520 cm^{-1}; δ_H ($CDCl_3$): 7.91 (s, 1H, H-6), 7.52 (br d, J=8 Hz, 2H, H-2′, -6′ or H-2‴, -6‴), 7.48 (br d, J=7 Hz, 2H, H-2′,6′ or H-2‴,6‴), 7.41 (br t, J=8 Hz, 2H, H-3′,5′ or H-3‴, 5‴), 7.37 (br t, J=7 Hz, 3H, H-3′,5′ or H-3‴,5‴ and H-4′ or H-4‴), 7.31 (br t, J=7 Hz, 1H, H-4′ or H-4‴), 5.37 (s, 2H, 2-CH_2), 3.87 (s, 3H, 5-OCH_3); δ_C ($CDCl_3$): 160.9, 154.7, 136.5, 130.4, 130.3, 129.0, 128.6, 128.4, 128.0, 127.9, 127.8, 121.7, 57.2, 55.6; MS (ESI): 91; HRMS (ESI) for $C_{18}H_{17}N_2O_2$ $[M+H]^+$: calcd 293.1290, found 293.1285.

3.2.2. 2-Benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one (6). The residue was purified by flash column chromatography on silica gel with CH_2Cl_2 as the eluent to yield the title compound as a pale yellow oil (603 mg, 88%); ν_{max} (KBr): 3441, 3058, 1645, 1601, 1494, 1425, 1336, 1254, 1025, 942, 755, 731, 697, 672, 654, 605 cm^{-1}; δ_H ($CDCl_3$): 7.76 (s, 1H, H-6), 7.60–6.90 (m, 14H), 5.50 (d, J=13.6 Hz, 1H, 2-CH_2, diastereotopic), 5.34 (d, J=13.6 Hz, 1H, 2-CH_2, diastereotopic); δ_C ($CDCl_3$): 160.0, 140.5, 139.9, 138.4, 136.38, 136.37, 133.0, 132.4, 131.2, 130.05, 130.01, 129.2, 128.6, 128.5, 128.0, 127.7, 127.5, 122.6, 56.1; MS (ESI): 417, 91; HRMS (ESI) for $C_{23}H_{18}BrN_2O$ $[M+H]^+$: calcd 417.0602, found 417.0617.

3.2.3. *N*-[2-(2-Benzyl-3-oxo-4-phenyl-2,3-dihydropyridazin-5-yl)phenyl]pivalamide (9). The residue was purified by flash column chromatography on silica gel with a mixture of ethyl acetate and CH_2Cl_2 (2.5:97.5) as the eluent and crystallized from ethyl acetate to yield the title compound as white needles (1.034 g, 89%); mp 227–229°C; ν_{max} (KBr): 3297, 3064, 2972, 1674, 1627, 1595, 1575, 1515, 1479, 1447, 1331, 1263, 1170, 959, 760, 730, 695 cm^{-1}; δ_H ($CDCl_3$): 7.76 (s, 1H, H-6), 7.65 (ddd, J=8.1, 1.0, 0.5 Hz, 1H, H-3″ or H-6″), 7.50 (br d, J=8 Hz, 2H, H-2′,6′ or H-2‴,6‴), 7.36–7.12 (m, 11H, H-3′,4′,5′,3″(or 6″),4″,5″,2‴(or 2′), 3‴, 4‴, 5‴, 6‴(or 6′)), 6.80 (br s, 1H, 1″-NH), 5.42 (two br s, 2H, 2-CH_2, diastereotopic), 1.07 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$): 176.5, 159.5, 138.6, 138.4, 138.1, 136.3, 134.3, 131.8, 130.2, 129.73, 129.72, 129.1, 128.9, 128.7, 128.6, 128.0, 127.9, 125.5, 124.6, 56.1, 39.4, 27.4; MS (ESI): 438, 91; HRMS (ESI) for $C_{28}H_{28}N_3O_2$ $[M+H]^+$: calcd 438.2182, found 438.2181.

3.2.4. 2-Benzyl-5-hydroxy-4-phenylpyridazin-3(2*H*)-one (4). A mixture of compound **3** (558 mg, 1.91 mmol), KOH (8.51 g, 152 mmol) and water (260 mL) was stirred and heated overnight under reflux in an oil bath (temperature of oil bath: 120°C). After cooling, the mixture was acidified with concentrated HCl and placed in a refrigerator for four hours. The precipitate was filtered, washed well with water until neutral and dried under vacuum to yield the title compound as a white powder (505 mg, 95%); mp 216–217°C; ν_{max} (KBr): 3062, 2701, 1627, 1580, 1552, 1497, 1453, 1377, 1318, 1276, 1164, 1054, 776, 756, 726, 698, 570 cm^{-1}; δ_H (DMSO-d_6): 11.15 (br s, 1H, 5-OH), 7.85 (s, 1H, H-6), 7.48 (br d, J=7 Hz, 2H, H-2′,6′), 7.37 (br t, J=7 Hz, 2H, H-3′,5′), 7.34–7.24 (m, 6H, H-4′,2‴,3‴,4‴,5‴,6‴), 5.23 (s, 2H, 2-CH_2); δ_C (DMSO-d_6): 160.4, 154.0, 137.2, 132.4, 131.1, 130.3, 128.4, 127.8, 127.4, 127.3, 117.0, 54.0; MS (ESI): 91; HRMS (ESI) for $C_{17}H_{15}N_2O_2$ $[M+H]^+$: calcd 279.1134, found 279.1133.

3.2.5. 2-Benzyl-4-phenyl-5-trifluoromethanesulfonyloxy-pyridazin-3(2*H*)-one (5). Compound **4** (465 mg, 1.67 mmol) and triethylamine (0.31 mL, 2.22 mmol) were dissolved in dry CH_2Cl_2 (12 mL) in a two-necked flask equipped with a drying tube and a septum, and placed in an ice-acetone bath (−5°C). Trifluoromethanesulfonic anhydride (0.31 mL, 1.84 mmol) was added dropwise to the cooled solution and stirred for 30 min at −5°C. The mixture was then poured onto 1 M HCl (8.5 mL) and water (50 mL) was added. Subsequently, the water phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with 1% $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated to dryness. The obtained oil (673 mg, 98%) was used in further transformations without purification and characterization.

3.2.6. 5-(2-Aminophenyl)-2-benzyl-4-phenylpyridazin-3(2*H*)-one (10). A mixture of compound **9** (200 mg,

0.457 mmol), ethanol (40 mL) and aqueous sulphuric acid (40% (v), 40 mL) was refluxed overnight. After cooling, water was added (40 mL) and the ethanol was evaporated under reduced pressure. The pH of the residue was adjusted to 8–9 by addition of aqueous ammonia (25%) during cooling. The mixture was then extracted with CH_2Cl_2 (5×40 mL), dried over $MgSO_4$, evaporated to dryness and crystallized from methanol to yield yellow prisms (146 mg, 90%); mp 138–139°C; ν_{max} (KBr): 3428, 3373, 3338, 3062, 3030, 2953, 1625, 1584, 1494, 1455, 1427, 1341, 1307, 1257, 1157, 1121, 1075, 1032, 939, 859, 797, 747, 724, 699, 639, 604, 574, 484 cm^{-1}; δ_H ($CDCl_3$): 7.80 (s, 1H, H-6), 7.57 (br dd, *J*=8, 1.5 Hz, 2H, H-2′,6′ or H-2‴,6‴), 7.38–7.19 (m, 8H, H-3′,4′,5′,2‴(or 2′),3‴,4‴,5‴,6‴ (or 6′)), 7.09 (ddd, *J*=8.1, 7.3, 1.5 Hz, 1H, H-4″ or H-5″), 6.89 (ddd, *J*=7.6, 1.5, 0.3 Hz, 1H, H-6″ or H-3″), 6.69 (ddd, *J*=7.7, 7.3, 1.1 Hz, 1H, H-5″ or H-4″), 6.57 (ddd, *J*=8.1, 1.1, 0.3 Hz, 1H, H-3″ or H-6″), 5.40 (two br s, 2H, 2-CH_2, diastereotopic), 3.45 (br s, 2H, 2″-NH_2); δ_C ($CDCl_3$): 159.8, 143.2, 139.1, 138.4, 136.4, 132.6, 130.1, 130.0, 129.8, 129.3, 128.8, 128.6, 128.0, 127.9, 120.6, 118.9, 116.2, 56.0; MS (ESI): 354, 91; HRMS (ESI) for $C_{23}H_{20}N_3O$ $[M+H]^+$: calcd 354.1606, found 354.1619.

3.3. General procedure for the synthesis of 2-benzyldibenzo[f,h]phthalazin-1(2*H*)-one (7) and 2-methyldibenzo[f,h]cinnolin-3(2*H*)-one (14) via intramolecular Pd-catalyzed arylation

A solution of compound **6** or **13** (**7**: 337 mg, 0.81 mmol; **14**: 621 mg, 1.82 mmol) in dimethyl acetamide (**7**: 8 mL; **14**: 15 mL) was flushed with N_2 for 5 min, NaOAc.$3H_2O$ (**7**: 220 mg, 1.62 mmol; **14**: 495 mg, 3.64 mmol), and $PdCl_2(PPh_3)_2$ (**7**: 113 mg, 0.16 mmol; **14**: 255 mg, 0.36 mmol) were added, and the mixture was stirred and heated under N_2 atmosphere in an oil bath at 130°C for 64 h (in the case of **7**) or 8 h (in the case of **14**). After cooling, the solvent was evaporated under reduced pressure and water (30 mL) was added. Subsequently, the mixture was extracted with CH_2Cl_2 or $CHCl_3$ (3×30 mL), dried over Na_2SO_4 or $MgSO_4$ and evaporated to dryness.

3.3.1. 2-Benzyldibenzo[f,h]phthalazin-1(2*H*)-one (7). The residue was subjected to flash column chromatography on silica gel with CH_2Cl_2 as the eluent to yield the title compound as white crystals (152 mg, 56%); mp 184–185°C; ν_{max} (KBr): 3027, 2952, 1636, 1584, 1496, 1443, 1374, 1262, 1227, 1166, 1072, 758, 729, 720, 699 cm^{-1}; δ_H ($CDCl_3$): 10.27 (dd, *J*=7.2, 2.6 Hz, 1H, H-12), 8.92 (s, 1H, H-4), 8.65 (br d, *J*=8 Hz, 1H, H-8), 8.64 (br d, *J*=10 Hz, 1H, H-9), 8.43 (ddd, *J*=8.2, 1.2, 0.6 Hz, 1H, H-5), 7.75 (m, 3H, H-7,10,11), 7.67 (ddd, *J*=8.2, 7.0, 1.2 Hz, 1H, H-6), 7.57 (br d, *J*=7 Hz, 2H, H-2‴,6‴), 7.37 (br t, 2H, *J*=7 Hz, H-3‴,5‴), 7.30 (tt, *J*=7.3, 1.4 Hz, 1H, H-4‴), 5.57 (s, 2H, 2-CH_2); δ_C ($CDCl_3$): 159.9 (C-1), 137.0 (C-1‴), 132.9 (C-4), 132.7 (C-8a), 131.4 (C-8b), 129.7 (C-7), 129.5 (C-12), 129.0 (C-10), 128.7 (C-2‴,6‴), 128.6 (C-3‴,5‴), 128.5 (C-4a), 128.12 (C-11), 128.09 (C-12a), 127.8 (C-4‴), 127.7 (C-6), 125.7 (C-4b), 123.9 (C-5), 123.6 (C-12b), 123.4 (C-8), 122.3 (C-9), 55.8 (2-CH_2); MS (ESI): 259, 231, 91; HRMS (ESI) for $C_{23}H_{17}N_2O$ $[M+H]^+$: calcd 337.1341, found 337.1334.

3.3.2. 2-Methyldibenzo[f,h]cinnolin-3(2*H*)-one (14). The residue was subjected to flash column chromatography on silica gel with a mixture of ethyl acetate and chloroform (1:9) as the eluent and recystallized from a mixture of chloroform and methanol to yield the title compound as yellow crystals (217 mg, 46%); mp 233–234°C; ν_{max} (KBr): 3440, 3057, 1650, 1594, 1563, 1490, 1449, 1271, 1233, 1007, 865, 759, 730, 710 cm^{-1}; δ_H ($CDCl_3$): 8.67 (dd, *J*=8.0, 1.4 Hz, 1H, H-12), 8.35 (br d, *J*=8.1 Hz, 1H, H-8), 8.28 (br d, *J*=8.1 Hz, 1H, H-9), 8.20 (br d, *J*=8.1 Hz, 1H, H-5), 7.71 (s, 1H, H-4), 7.68 (ddd, *J*=8.3, 7.2, 1.2 Hz, 1H, H-7), 7.61 (ddd, *J*=8.1, 7.1, 1.5 Hz, 1H, H-10), 7.55 (br t, 2H, H-6,11), 4.07 (s, 3H, 2-CH_3); δ_C ($CDCl_3$): 161.0 (C-3), 137.5 (C-12b), 134.5 (C-4a), 132.1 (C-8a), 131.3 (C-7), 130.7 (C-8b), 129.7 (C-10), 128.6 (C-11), 128.4 (C-6), 128.3 (C-12a), 126.3 (C-4b), 125.1 (C-5), 124.1 (C-12), 123.8 (C-8), 123.2 (C-9), 118.9 (C-4), 41.1 (2-CH_3); MS (ESI): 218, 189, 165; HRMS (ESI) for $C_{17}H_{13}N_2O$ $[M+H]^+$: calcd 261.1028, found 261.1028.

3.4. General procedure for the synthesis of 2-benzyldibenzo[f,h]phthalazin-1(2*H*)-one (7) and 2-methyldibenzo[f,h]cinnolin-3(2*H*)-one (14) via Pschorr reaction

Compound **10** or **15** (**7**: 104 mg, 0.294 mmol; **14**: 440 mg, 1.6 mmol) was dissolved in concentrated HCl (**7**: 6 mL; **14**: 13 mL) and cooled to 0°C while stirring. Aqueous $NaNO_2$ solution (**7**: 61 mg, 0.882 mmol in 3 mL of water; **14**: 235 mg, 3.4 mmol in 9 mL of water) was added dropwise at such a rate that the temperature of the mixture did not exceed 5°C. The reaction mixture was stirred further at this temperature for 1.5 h, and at room temperature for an additional 1.5 h. Subsequently, the mixture was neutralized using a saturated Na_2CO_3 solution, extracted with CH_2Cl_2 or $CHCl_3$ (3×20 mL), dried over Na_2SO_4 or $MgSO_4$ and evaporated to dryness.

3.4.1. 2-Benzyldibenzo[f,h]phthalazin-1(2*H*)-one (7). The residue was purified by flash column chromatography on silica gel with CH_2Cl_2 as the eluent to yield the title compound as white crystals (69 mg, 70%).

3.4.2. 2-Methyldibenzo[f,h]cinnolin-3(2*H*)-one (14). The residue was recrystallized from a mixture of chloroform and methanol to yield the title compound as yellow crystals (265 mg, 64%).

3.4.3. Dibenzo[f,h]phthalazin-1(2*H*)-one (8). A mixture of compound **7** (101 mg, 0.3 mmol), $AlCl_3$ (240 mg, 1.8 mmol) and toluene (10 mL) was stirred and heated at 70°C for 1 h (the reflux condenser was equipped with a drying tube). After cooling, water was added (10 mL) and the mixture was extracted with $CHCl_3$ (6×30 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to flash column chromatography on silica gel with a mixture of methanol and toluene (5:95) as the eluent to yield the title compound as white-pink crystals (43 mg, 58%); mp 325°C (decomp.); ν_{max} (KBr): 3440, 3155, 3036, 2917, 1644, 1558, 1449, 1248, 1159, 1141, 1010, 879, 782, 762, 737, 722 cm^{-1}; δ_H (DMSO-d_6): 13.27 (br s, 1H, 2-H), 10.27 (dd, *J*=8.4, 1.3 Hz, 1H, H-12), 9.35 (s, 1H, H-4), 9.00–8.92 (three br d, 3H, H-5,8,9), 7.96–7.79 (four br t,

4H, H-6,7,10,11); δ_C (DMSO-d_6): 160.6, 133.8, 132.0, 130.8, 130.1, 129.01, 128.98, 128.4, 128.0, 127.9, 127.3, 125.5, 125.1, 123.6, 123.0, 122.4; MS (ESI): 247, 229, 218, 204, 190, 177, 165; HRMS (ESI) for $C_{16}H_{11}N_2O$ $[M+H]^+$: calcd 247.0871, found 247.0872.

3.4.4. 5-(2-Bromophenyl)-2-methyl-6-phenylpyridazin-3(2*H*)-one (13). A mixture of compound **12** (441 mg, 2 mmol) and $Pd(PPh_3)_4$ (120 mg, 0.1 mmol) in dimethoxyethane (12 mL) was stirred for 20 min under N_2 atmosphere at room temperature. 2-Bromophenylboronic acid (500 mg, 2.5 mmol) and aqueous Na_2CO_3 (2 M, 2 mL) were added and the mixture was stirred and refluxed in an oil bath (temperature oil bath: 110°C) under a N_2 atmosphere for 5 h. After cooling, the reaction mixture was poured onto ice-water (30 mL), extracted with CH_2Cl_2 (3×30 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with a mixture of ethyl acetate and hexane (1:4) as the eluent and recrystallized from methanol to yield the title compound as white crystals (424 mg, 62%); mp 151–152°C; ν_{max} (KBr): 3047, 2948, 1666, 1594, 1574, 1561, 1491, 1471, 1442, 1425, 1392, 1326, 1263, 1158, 1003, 994, 952, 901, 797, 778, 762, 745, 728, 701, 656, 568 cm^{-1}; δ_H ($CDCl_3$): 7.51 (ddd, J=7.9, 1.2, 0.3 Hz, 1H, H-3″), 7.29 (td, J=7.5, 1.2 Hz, 1H, H-5″), 7.27–7.18 (m, 5-H, H-2′,3′,4′,5′,6′), 7.20 (td, J=7.7, 1.7 Hz, 1H, H-4″), 7.16 (ddd, J=7.6, 1.7, 0.3 Hz, 1H, H-6″), 6.90 (s, 1H, H-4), 3.93 (s, 3H, 2-CH_3); δ_C ($CDCl_3$): 160.0, 146.0, 145.0, 137.1, 135.3, 133.1, 130.6, 130.3, 129.9, 128.8, 128.6, 128.0, 127.5, 122.3, 40.3; MS (ESI): 282, 261, 259, 247, 233, 220, 204, 203, 181, 144, 133, 130, 118, 102, 77; HRMS (ESI) for $C_{17}H_{14}BrN_2O$ $[M+H]^+$: calcd 341.0289, found 341.0283.

Acknowledgements

Dr P. Tapolcsányi thanks the RAFO RUCA for a post-doctoral grant. Professor Dr B. U. W. Maes is grateful to the FWO-Flanders for financial support to perform a research stay in Budapest. Funding by RAFO RUCA, OTKA 33105, OTKA 31910 and ETT 187/2000 is gratefully acknowledged. The authors wish to thank Professor Dr E. Esmans and Professor Dr F. Lemière for the use of their MS facilities and Ing. J. Aerts, J. Schrooten, R. Tuytten, Ing. W. Van Dongen and Ing. J. Verreydt for technical assistance.

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