Pergamon

Tetrahedron 58 (2002) 5645–5650

TETRAHEDRON

Synthesis of new pyridazino[4,5-*c*]isoquinolinones by Suzuki cross-coupling reaction

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Cordially dedicated to Professor András Messmer on the occasion of his 80th birthday

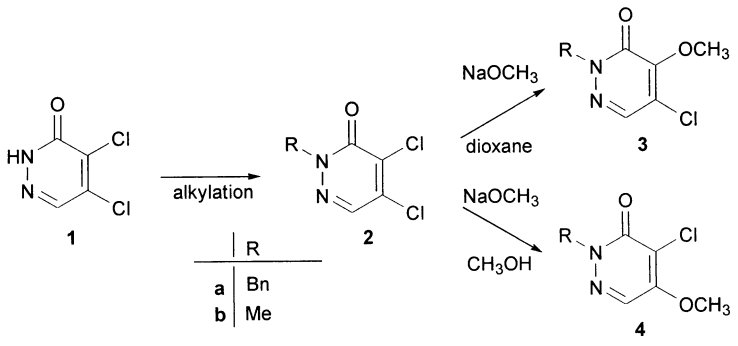
Received 14 February 2002; revised 7 May 2002; accepted 23 May 2002

Abstract—Suzuki cross-coupling reaction of 2-alkyl(methyl and benzyl)-5-chloro-4-methoxy- and 2-alkyl(methyl and benzyl)-4-chloro-5-methoxypyridazin-3(2*H*)-ones with 2-formylphenylboronic acid afforded the corresponding biaryl products which were cyclized with ammonia to yield hitherto undescribed pyridazino[4,5-*c*]isoquinolinones. Removal of the *N*-benzyl protective group in position 2 yielded the unsubstituted tricyclic pyridazinones.

Recently, we have reported that Suzuki coupling of 5-iodo-2-methylpyridazin-3(2*H*)-one with 2-aminophenylboronic acids yielded new biaryl compounds that proved to be appropriate starting material for a ring closure procedure towards the synthesis of new tricyclic aza-β-carbolines.[1] Furthermore, one of our most recent publications revealed that the palladium catalysed Suzuki cross-coupling methodology can widely be applied on chloropyridazin-3(2*H*)-ones, thereby allowing an easy access to a series of new arylpyridazin-3(2*H*)-ones.[2]

As a continuation of these studies, we probed new synthetic strategies towards the synthesis of tricylic fused pyridazinones, based upon Suzuki cross-coupling reactions[3] on easily accessible chloromethoxypyridazin-3(2*H*)-ones. In this paper, we report the synthesis of hitherto unknown pyridazino[4,5-*c*]isoquinolin-4(3*H*)-ones and pyridazino-[4,5-*c*]isoquinolin-1(2*H*)-ones based upon palladium catalysed cross-coupling of commercially available 2-formylphenylboronic acid with 2-substituted 4-chloro-5-methoxy and 5-chloro-4-methoxypyridazin-3(2*H*)-ones.

The synthetic procedure leading to the chloromethoxypyridazinones is shown in Scheme 1. First, the cheap, commercially available 4,5-dichloropyridazin-3(2*H*)-one (**1**) was N-alkylated yielding 2-benzyl-4,5-dichloropyridazin-3(2*H*)-one (**2a**) and 2-methyl-4,5-dichloropyridazin-3(2*H*)-one (**2b**).[4–8] Suzuki cross-coupling of arylboronic



Scheme 1.

Keywords: palladium; Suzuki reaction; tricyclic pyridazinones; ring closure; debenzylation.

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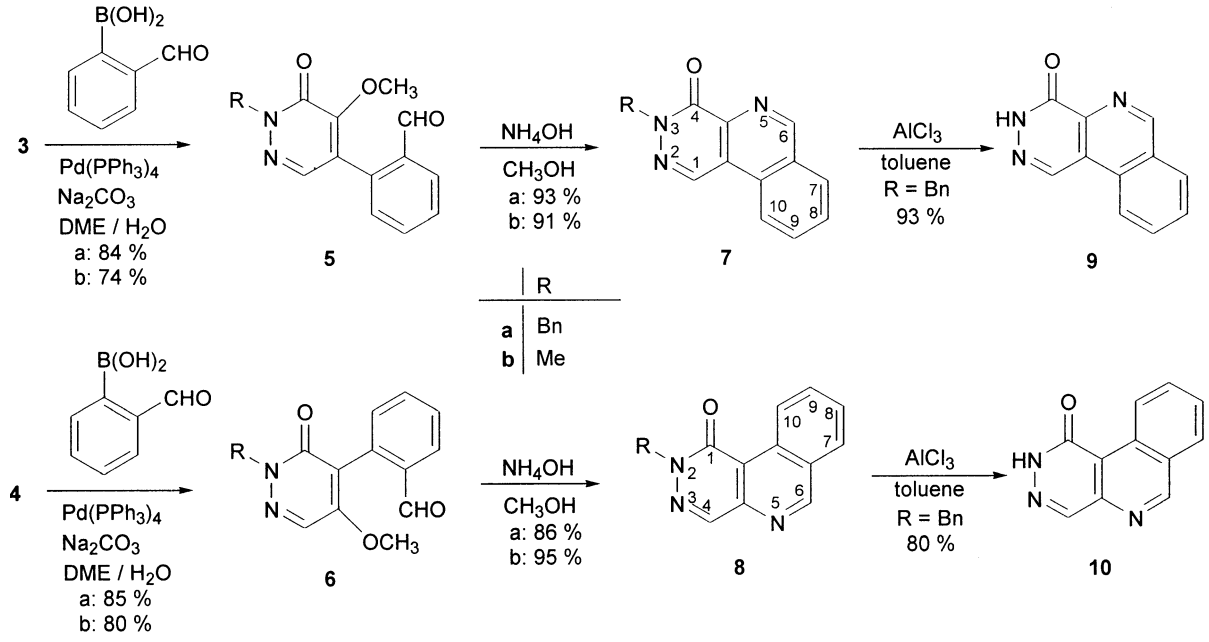

Scheme 2.

acids with these 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones gives a mixture of two monoaryl isomers.[2] Usually, diarylated reaction product is formed depending on the boronic acid used.[2] Recently, we described a similar non-selective behaviour in Sonogashira reactions on 4,5-dichloro-2-methylpyridazin-3(2*H*)-one.[9] Because of this selectivity problem, a chlorine atom is now replaced by a methoxy group as a provisionally masked functionality. The choice for a methoxy group is obvious since we[2] and others[4,5,10] reported earlier that the chlorine substituents of 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones can be selectively replaced with sodium methanolate, depending on the choice of the solvent. Reactions in solvents with high dielectric constant (e.g. methanol) give the 5-methoxy derivative (**4**)[4,5,10] whereas solvents with low dielectric constant (e.g. dioxane) favour formation of the 4-methoxy compound **3**.[2,10]

Then, we studied the introduction of the 2-formylphenyl group on **3** and **4** via Suzuki cross-coupling reaction (Scheme 2). Pyridazinone **4a** was chosen as the test substrate. Recently, we described that the *ortho* substituted boronic acid 2,4-dichlorophenylboronic acid can be coupled in high yield with 2-methyl-4-chloro-5-methoxypyridazin-3(2*H*)-one (**4b**) in a two phase system of toluene/2 M aqueous Na_2CO_3 solution in high yield using a large excess of the boronic acid and tetrakis(triphenylphosphine)palladium as a catalyst.[2] However, for the coupling of **4a** with 2-formylphenylboronic acid (3 equiv.) similar reaction conditions were not suitable since a large amount of starting material was still present after one day of reflux as shown by TLC and DCI-MS analysis. Therefore, we focused on the use of Gronowitz coupling conditions which have proven to be beneficial when phenylboronic acids with electron withdrawing groups in the *ortho* position are used due to a reduced hydrolytic deboronation side reaction of the boronic acids.[11,12] Thus, **4a**, 2-formylphenylboronic acid (3 equiv.) and tetrakis(triphenylphosphine)palladium were heated in a mixture of DME and 10% aqueous Na_2CO_3 solution. However, some starting material remained unconsumed even after two days of reflux. Finally, we found that stepwise addition of the boronic acid (3 equiv.) resulted in a complete reaction after 24 h yielding **6a** in 85%. This beneficial effect of gradual addition, probably suppresses the unwanted deboronation of the 2-formylphenylboronic acid which most likely is responsible for the incomplete reaction when the boronic acid is added at once. For the synthesis of the isomer **5a**, a smaller excess of boronic acid was required. Compounds **5b** and **6b** were prepared under the same reaction conditions as **5a** and **6a**, respectively.

Finally, when **5a**, **5b**, **6a** and **6b** were refluxed for a short time (30 min) in a mixture of methanol and concentrated aqueous ammonia, a ring closure to the tricyclic pyridazinones **7a**, **7b**, **8a** and **8b**, respectively occurred. To the best of our knowledge, these tricyclic pyridazinones represent a new group of heterocyclic compounds. Although the pyridazino[4,5-*c*]isoquinoline ring system has been prepared by an entirely different procedure,[13] no publication has yet appeared on the synthesis of the pyridazino[4,5-*c*]-isoquinolinones **7**–**10**.

An interesting aspect of our new synthetic strategy is the rationalization of the mechanism of the ring closure (Fig. 1). An obvious interpretation would be that the first step is the nucleophilic displacement of the methoxy group with an amino moiety (i.e. formation of **A**) followed by a condensation of the amino and formyl groups to give **9**. However, attempts to transform related 4- and 5-methoxy derivatives (2-methyl-4-methoxy-5-phenylpyridazin-3(2*H*)-one and its isomer 2-methyl-5-methoxy-4-phenylpyridazin-3(2*H*)-one) into the corresponding amino derivatives under the same reaction conditions as used for the ring closure procedure were unsuccessful. This observation is in agreement with literature data that indicate that methoxypyridazin-3(2*H*)-ones are unreactive towards intermolecular substitution by

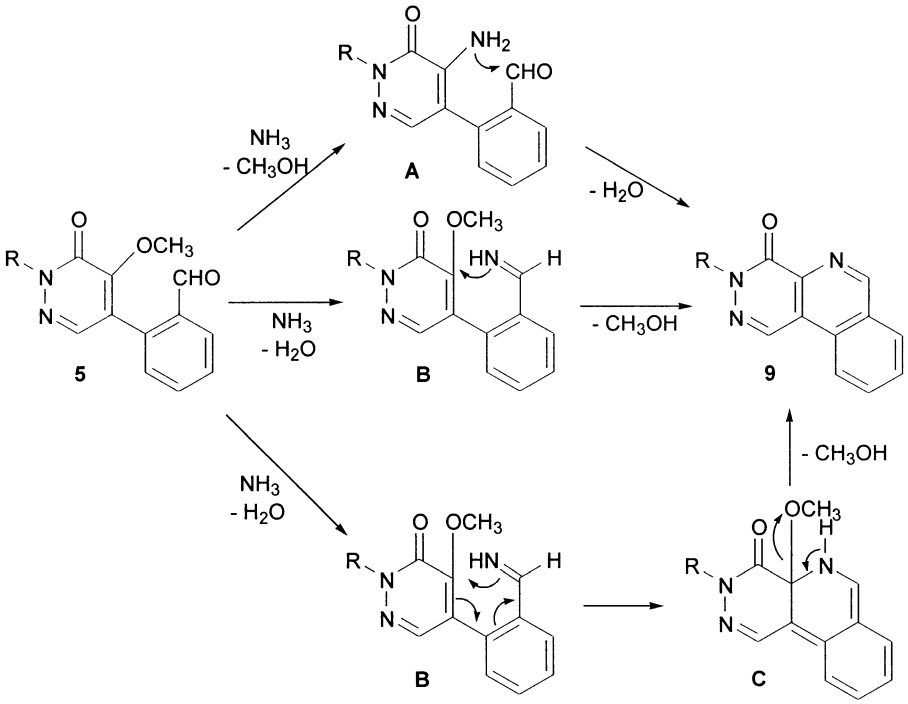

Figure 1.

amines (even under forced conditions, e.g. with morpholine at elevated temperature).[14,20] Instead, demethylation into hydroxypyridazin-3(2*H*)-ones is observed in these cases. Based on these test experiments and literature data we believe that the cyclization consists of imine (**B**) formation followed by nucleophilic displacement of the methoxy group (**B→9**) rather than the reverse sequence. Since an imine is a rather weak nucleophile, the good leaving group properties of the methoxy group must be ascribed to the formation of the new aromatic ring as the driving force for the irreversible cyclization. Another possibility for the ring closure of the proposed imine intermediate **B** is that an electrocyclic reaction takes place (**B→C**) followed by elimination of methanol (**C→9**). Clarification of the exact reaction mechanism will be the subject of further studies.

Study of the reactivity of **7** and **8** revealed that in the case of the *N*-benzyl derivatives (**7a** and **8a**) the benzyl group could be smoothly removed with aluminium trichloride to yield the unsubstituted fused pyridazinones **9** and **10** (Scheme 2).[15–19] This transformation seems to be of particular synthetic interest, since further transformation of the lactam moiety allows valuable functionalization of these products. Study of the reactivity of these tricylic pyridazinones as well as biological studies on the new compounds is in progress.

1. Experimental

1.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer (only the ^{1}H and ^{13}C NMR spectra of **5b** and **6b** were measured on a 200 MHz machine) in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Nicolet Magna 750 FT-IR (**5b**, **6b**, **7b** and **8b**) or a Bruker Vector 22 spectrometer (**2a**, **3a**, **4a**, **5a**, **6a**, **7a**, **8a**, **9** and **10**). For mass spectrometric analysis, samples were dissolved in methanol 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 methanol (0.1% formic acid), using the CapLC HPLC system (Waters, Millford). Product ion spectra were recorded, and exact masses were measured on a quadrupole/orthogonal-acceleration time-of-flight (Q/oaTOF) tandem mass spectrometer (qTOF 2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (35 V) and capillary voltage (3.3 kV) were optimised on one compound and used for the series of experiments. Fragmentation was induced by low energy collisional activation using Ar gas and a collision energy of 15 eV. 4,5-Dichloro-2-methylpyridazin-3(2*H*)-one[5] (**2b**), 4-chloro-5-methoxy-2-methylpyridazin-3(2*H*)-one[5] (**4b**) and 5-chloro-4-methoxy-2-methylpyridazin-3(2*H*)-one[2a] (**3b**) were synthesized via literature procedures. $Pd(PPh_3)_4$ (Acros), 4,5-dichloropyridazin-3-(2*H*)-one (Aldrich) and 2-formylphenylboronic acid (Lancaster) were obtained from commercial sources. Flash column chromatography was performed on Kieselgel 60 (Merck), 0.040–0.063 mm.

1.1.1. Synthesis of 2-benzyl-4,5-dichloropyridazin-3(2*H*)-one (2a). A mixture of 4,5-dichloropyridazin-3(2*H*)-one (**1**) (6.0 mmol, 0.99 g), benzyl bromide (6.3 mmol, 1.08 g), potassium carbonate (15.0 mmol, 2.07 g), tetrabutylammonium bromide (0.3 mmol, 0.1 g) and

acetonitrile (15 mL) was stirred and heated under reflux for 1 h (the reflux condenser was equipped with a drying tube). After cooling, the solvent was evaporated under reduced pressure. The residue was purified by filtration on a small silica gel column with dichloromethane as the eluent, yielding the title compound (1.24 g, 81%); mp 85°C (white solid); ν_{max} (KBr): 1649, 1578, 1418, 1288, 1222, 969, 952, 897, 723, 694 cm^{-1}; δ_H (DMSO-d_6): 8.23 (s, 1H, H-6), 7.27–7.37 (m, 5H, Ph), 5.29 (s, 2H, CH_2); δ_C (DMSO-d_6): 155.7, 136.1, 136.1, 135.7, 133.1, 128.6, 128.0, 127.7, 55.4; LRMS (ESI): 255.0, 91.1; HRMS (ESI) for $C_{11}H_9Cl_2N_2O$ $[M+H]^+$ found: 255.0089 calcd: 255.0092.

1.1.2. Synthesis of 2-benzyl-5-chloro-4-methoxypyridazin-3(2*H*)-one (3a). To a magnetically stirred solution of 2-benzyl-4,5-dichloropyridazin-3(2*H*)-one (**2a**) (4.47 mmol, 1.14 g) in dry dioxane (20 mL) was added 1.0 mL of a 4.86 M $NaOCH_3$ solution. The solution was stirred at room temperature for 1 h (the flask was equipped with a drying tube) and then poured into 100 mL H_2O/150 mL CH_2Cl_2. The organic layer was separated and dried on $MgSO_4$ and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with CH_2Cl_2 as the eluent; yield: 0.83 g, 74% (oil); ν_{max} (liquid film): 1638, 1587, 1455, 1311, 1260, 1028, 951, 727, 699, 618 cm^{-1}; δ_H (DMSO-d_6): 8.04 (s, 1H, H-6), 7.26–7.36 (m, 5H, Ph), 5.25 (s, 2H, CH_2), 4.16 (s, 3H, OCH_3); δ_C (DMSO-d_6): 156.4, 150.9, 137.5, 136.2, 128.4, 127.9, 127.6, 122.4, 60.2, 54.3; LRMS (ESI): 251.1, 91.1; HRMS (ESI) for $C_{12}H_{12}ClN_2O_2$ $[M+H]^+$ found: 251.0594 calcd: 251.0587.

1.1.3. Synthesis of 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one (4a). To a magnetically stirred solution of 2-benzyl-4,5-dichloropyridazin-3(2*H*)-one (**2a**) (4.47 mmol, 1.14 g) in dry methanol (20 mL) was added 1.3 mL of a 4.86 M $NaOCH_3$ solution. The solution was stirred at room temperature for 1 h (the flask was equipped with a drying tube) and then poured into 100 mL H_2O/150 mL CH_2Cl_2. The organic layer was separated and dried over $MgSO_4$ and evaporated to dryness yielding the title compound (0.95 g, 85%); mp 94°C (white solid); ν_{max} (KBr): 1638, 1601, 1457, 1407, 1315, 1282, 1207, 1172, 942, 875, 749, 700, 516 cm^{-1}; δ_H (DMSO-d_6): 8.28 (s, 1H, H-6), 7.26–7.36 (m, 5H, Ph), 5.29 (s, 2H, CH_2), 4.07 (s, 3H, OCH_3); δ_C (DMSO-d_6): 157.5, 155.2, 136.4, 128.4, 128.0, 127.9, 127.6, 114.3, 58.1, 54.8; LRMS (ESI): 251.1, 91.1; HRMS (ESI) for $C_{12}H_{12}ClN_2O_2$ $[M+H]^+$ found: 251.0583 calcd: 251.0587.

1.2. General procedure for the Suzuki cross-coupling reaction (5a, 5b, 6a, 6b)

The pyridazin-3(2*H*)-ones **3a**, **3b**, **4a** or **4b** (2.0 mmol) were dissolved in dimethoxyethane (12 mL). $Pd(PPh_3)_4$ (0.10 mmol, 0.12 g) was added at room temperature under an argon flow. After stirring at room temperature for 10 min, 2-formylphenylboronic acid (3.2 mmol, 0.480 g) and aq. Na_2CO_3 (10 wt%, 2 mL) were added. Subsequently, the reaction mixture was refluxed (oil bath temperature: 110°C) with stirring under argon atmosphere (reaction time: **3a** and **3b** 6 h, **4a** and **4b** 24 h). After 3 h of reflux, an additional portion of 2-formylphenylboronic acid (0.80 mmol, 0.120 g) was added. For the syntheses with **4a** and **4b** also after 6 and 12 h 1.0 mmol portions boronic acid was added. The cooled reaction mixture was poured onto 30 mL of H_2O and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried on $MgSO_4$, filtered, and the filtrate evaporated to dryness. The residue was purified by flash column chromatography on silica gel with CH_2Cl_2–CH_3OH (100:1 for **5a** and **5b**, 100:0.5 for **6a** and **6b**) as the eluent.

1.2.1. 2-(1-Benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde (5a). Yield: 0.54 g, 84%; mp 132°C (white solid); ν_{max} (KBr): 1704, 1635, 1597, 1516, 1453, 1336, 1308, 1256, 1202, 1021, 934, 767, 743, 698 cm^{-1}; δ_H (DMSO-d_6): 9.92 (d, $J\cong0.3$ Hz, 1H, CHO), 7.97 (br dd, $J=7.6$, ~1.1 Hz, 1H, H-6), 7.89 (s, 1H, H-3′), 7.78 (dt, $J=7.5$, 1.4 Hz, 1H, H-4), 7.67 (br dt, $J\cong7.0$, ~0.6 Hz, 1H, H-5), 7.49 (br dd, $J=7.6$, ~0.9 Hz, 1H, H-3), 7.28–7.41 (m, 5H, Ph), 5.32 (br s, 2H, CH_2), 3.90 (s, 3H, OCH_3); δ_C (DMSO-d_6): 191.9, 156.8, 151.2, 138.5, 136.59, 133.9, 133.8, 133.5, 130.6, 129.4, 129.2, 128.4, 128.0, 127.5, 126.3, 59.6, 54.3; LRMS (ESI): 321.2, 91.1; HRMS (ESI) for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ found: 321.1233 calcd: 321.1239.

1.2.2. 2-(5-Methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde (5b). Yield: 0.36 g, 74%; mp 114–116°C (white solid); ν_{max} (KBr): 3065, 3011, 2940, 1692, 1648, 1600, 1521, 1442, 1408, 1305, 1202, 1045, 997, 921, 757 cm^{-1}; δ_H ($CDCl_3$): 9.92 (s, 1H, CHO), 8.01 (d, $J=$ 7.6 Hz, 1H, H-6), 7.70 (dt, $J=7.3$, 1.3 Hz, 1H, H-4), 7.64 (s, 1H, H-3′), 7.58 (t, $J=7.5$ Hz, 1H, H-5), 7.32 (d, $J=$ 7.3 Hz, 1H, H-3), 4.05 (s, 3H, OCH_3), 3.85 (s, 3H, NCH_3); δ_C ($CDCl_3$): 190.6, 137.8, 133.8, 133.6, 130.1, 129.3, 129.2, 60.2, 40.1; LRMS (ESI): 245.1; HRMS (ESI) for $C_{13}H_{13}N_2O_3$ $[M+H]^+$ found: 245.0931 calcd: 245.0926.

1.2.3. 2-(2-Benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)benzaldehyde (6a). Yield: 0.54 g, 85%; mp 108°C (white solid); ν_{max} (KBr): 1693, 1622, 1597, 1274, 1246, 1160, 703 cm^{-1}; δ_H (DMSO-d_6): 9.76 (d, $J=0.6$ Hz, 1H, CHO), 8.34 (s, 1H, H-6′), 7.90 (ddd, $J=7.6$, 1.4, 0.5 Hz, 1H, H-6), 7.70 (dt, $J=7.6$, 1.4 Hz, 1H, H-4), 7.57 (tdd, $J=$ 7.6, 1.2, 0.6 Hz, 1H, H-5), 7.40 (ddd, $J=7.8$, 1.2, 0.5 Hz, 1H, H-3), 7.26–7.37 (m, 5H, Ph), 5.27 and 5.32 (2×br d, $J\cong14.1$ Hz, 2H, CH_2 diastereotopic), 3.91 (s, 3H, OCH_3); δ_C (DMSO-d_6): 191.5, 160.0, 155.6, 136.8, 134.1, 133.4, 133.3, 131.7, 128.9, 128.6, 128.4, 127.8, 127.7, 127.4, 117.5, 57.5, 54.2; LRMS (ESI): 321.2; HRMS (ESI) for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ found: 321.1254 calcd: 321.1239.

1.2.4. 2-(5-Methoxy-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)benzaldehyde (6b). Yield: 0.39 g, 80%; mp 163–165°C (white solid); ν_{max} (KBr): 3054, 2952, 2855, 1690, 1626, 1593, 1389, 1275, 1193, 1165, 965, 784, 760, 723, 696, 538 cm^{-1}; δ_H ($CDCl_3$): 9.82 (s, 1H, H-CHO), 7.97 (dd, $J=7.5$, 1.3 Hz, 1H, H-6), 7.90 (s, 1H, H-3′), 7.64 (dt, $J=7.4$, 1.5 Hz, 1H, H-4), 7.51 (t, $J=7.4$ Hz, 1H, H-5), 7.32 (dd, $J=7.5$, 1.3 Hz, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, NCH_3); δ_C ($CDCl_3$): 190.9, 155.6, 134.2, 133.4, 131.3, 128.8, 128.7, 126.7, 57.1, 40.4; LRMS (ESI): 245.1,

217.1; HRMS (ESI) for $C_{13}H_{13}N_2O_3$ $[M+H]^+$ found: 245.0938 calcd: 245.0926.

1.3. General procedure for the ring closure of 5 and 6

A mixture of pyridazin-3(2*H*)-one (**5** or **6**, 2.0 mmol), CH_3OH (40 mL) and NH_4OH (20 mL, 28–30 wt%) was heated at 60°C for 0.5 h. After cooling, the precipitate was filtered off and rinsed well with CH_3OH (30 mL).

1.3.1. 3-Benzylpyridazino[4,5-*c*]isoquinolin-4(3*H*)-one (7a). Yield: 0.53 g, 93%; mp 240°C (white solid); ν_{max} (KBr): 1659, 1586, 1344, 773, 669 cm^{-1}; δ_H (DMSO-d_6): 9.67 (d, *J*=0.8 Hz, 1H, H-6), 9.33 (s, 1H, H-1), 8.90 (br dd, *J*=8.4, 0.8 Hz, 1H, H-10), 8.41 (br ddd, *J*=8.1 Hz, 1H, H-7), 8.12 (ddd, *J*=8.4, 7.0, ~1.3 Hz, 1H, H-9), 8.02 (ddd, *J*=8.1, 7.0, ~1.1 Hz, 1H, H-8), 7.38 (br d, 2H, *o*-Ph), 7.34 (br t, 2H, *m*-Ph), 7.28 (br t, 1H, *p*-Ph), 5.45 (s, 2H, CH_2); δ_C (DMSO-d_6): 158.1, 157.1, 138.6, 137.1, 133.5, 132.8, 130.5, 129.7, 129.0, 128.7, 128.4, 127.8, 127.4, 123.3, 121.9, 54.3; LRMS (ESI): 288.1, 106.1, 91.1; HRMS (ESI) for $C_{18}H_{14}N_3O$ $[M+H]^+$ found: 288.1146 calcd: 288.1137.

1.3.2. 3-Methylpyridazino[4,5-*c*]isoquinolin-4(3*H*)-one (7b). Yield: 0.38 g, 91%; mp 287–295°C (white solid); ν_{max} (KBr): 3062, 3043, 1656, 1580, 1341, 939, 786, 769, 696 cm^{-1}; δ_H ($CDCl_3$): 9.56 (d, *J*=0.7 Hz, 1H, H-6), 8.86 (s, 1H, H-1), 8.51 (dd, *J*=7.5, 0.7 Hz, 1H, H-10), 8.19 (dd, *J*=7.8, 1.4 Hz, 1H, H-7), 8.02 (ddd, *J*=7.5, 7.1, ~1.3 Hz, 1H, H-9), 7.91 (ddd, *J*=7.8, 7.1, ~1.4 Hz, 1H, H-8), 4.01 (s, 3H, NCH_3); δ_C ($CDCl_3$): 159.7 (C-4), 157.3 (C-6), 139.3 (C-4a), 132.9 (C-9), 132.1 (C-1), 130.4 (C-8), 130.3 (C-10a), 129.4 (C-7), 129.3 (C-6a), 122.6 (C-10), 122.2 (C-1a), 40.5 (NCH_3); LRMS (ESI): 212.1; HRMS (ESI) for $C_{12}H_{10}N_3O$ $[M+H]^+$ found: 212.0824 calcd: 212.0824.

1.3.3. 2-Benzylpyridazino[4,5-*c*]isoquinolin-1(2*H*)-one (8a). Yield: 0.49 g, 86%; mp 173°C (white solid); ν_{max} (KBr): 1643, 1495, 772, 751, 717, 697, 513 cm^{-1}; δ_H (DMSO-d_6): 9.82 (ddd, *J*=8.5, ~1.1, ~0.7 Hz, 1H, H-10), 9.76 (d, *J*≅0.7 Hz, 1H, H-6), 8.67 (s, 1H, H-4), 8.41 (br ddd, *J*=8.1, ~1.4, ~0.7 Hz, 1H, H-7), 8.12 (ddd, *J*=8.5, 7.0, ~1.4 Hz, 1H, H-9), 8.00 (ddd, *J*=8.1, 7.0, ~1.1 Hz, 1H, H-8), 7.40 (br d, 2H, *o*-Ph), 7.34 (br t, 2H, *m*-Ph), 7.28 (br t, 1H, *p*-Ph), 5.49 (s, 2H, CH_2); δ_C (DMSO-d_6): 159.9, 159.5, 143.0, 139.2, 137.0, 133.5, 131.2, 129.7, 129.2, 128.5, 128.4, 127.8, 127.4, 126.3, 117.3, 54.4; LRMS (ESI): 288.1, 106.1; HRMS (ESI) for $C_{18}H_{14}N_3O$ $[M+H]^+$ found: 288.1138 calcd: 288.1137.

1.3.4. 2-Methylpyridazino[4,5-*c*]isoquinolin-1(2*H*)-one (8b). Yield: 0.40 g, 95%; mp 149–151°C (white solid); ν_{max} (KBr): 3124, 3058, 3033, 2989, 1645, 1578, 1551, 1500, 1436, 1398, 1241, 1011, 902, 814, 792, 767 cm^{-1}; δ_H ($CDCl_3$): 9.98 (d, *J*=8.4 Hz, 1H, H-10), 9.53 (s, 1H, H-6), 8.55 (s, 1H, H-4), 8.15 (d, *J*=8.1 Hz, 1H, H-7), 8.04 (ddd, *J*=8.1, 7.0, ~1.5 Hz, 1H, H-9), 7.88 (ddd, *J*=8.1, 7.0, ~1.1 Hz, 1H, H-8), 4.00 (s, 3H, NCH_3); δ_C ($CDCl_3$): 161.4 (C-1), 159.5 (C-6), 143.8 (C-4a), 139.3 (C-4), 133.6 (C-9), 132.5 (C-10a), 129.8 (C-8), 128.7 (C-7), 127.8 (C-10), 127.6 (C-6a), 118.5 (C-1a), 40.5 (NCH_3); LRMS (ESI): 212.1; HRMS (ESI) for $C_{12}H_{10}N_3O$ $[M+H]^+$ found: 212.0816 calcd: 212.0824.

1.4. General procedure for the debenzylation of 7a and 8a

A mixture of pyridazinoisoquinolinone (**7a** or **8a**, 1.0 mmol), $AlCl_3$ (6.0 mmol, 0.8 g) and toluene (30 mL) was stirred and heated at 70°C for 1 h (the reflux condenser was equipped with a drying tube). After cooling, H_2O (5 mL) was added. Subsequently, the mixture was filtered and rinsed well with H_2O (80 mL). The residue was purified by flash column chromatography on silica gel.

1.4.1. Pyridazino[4,5-*c*]isoquinolin-4(3*H*)-one (9). Yield: 0.18 g, 93%; eluent for flash column chromatography: CH_2Cl_2–CH_3OH (9:1); mp >300°C (decomp.) (white solid); ν_{max} (KBr): 3154, 3022, 2921, 2873, 1660, 1556, 1341, 1232, 842, 766, 718 cm^{-1}; δ_H (DMSO-d_6): 9.65 (d, *J*≅0.6 Hz, 1H, H-6), 9.25 (s, 1H, H-1), 8.89 (br dd, *J*=8.4, ~0.6 Hz, 1H, H-10), 8.40 (br dd, *J*=8.1, ~0.8 Hz, 1H, H-7), 8.11 (ddd, *J*=8.4, 7.0, 1.4 Hz, 1H, H-9), 8.01 (ddd, *J*=8.1, 7.0, 1.1 Hz, 1H, H-8); δ_C (DMSO-d_6): 159.3, 156.7, 139.0, 133.7, 132.7, 130.4, 129.7, 129.0, 128.9, 123.4, 122.5; LRMS (ESI): 198.1; HRMS (ESI) for $C_{11}H_8N_3O$ $[M+H]^+$ found: 198.0669 calcd: 198.0667.

1.4.2. Pyridazino[4,5-*c*]isoquinolin-1(2*H*)-one (10). Yield: 0.15 g, 80%; eluent for flash column chromatography: CH_2Cl_2–CH_3OH (95:5); mp >300°C (decomp.) (white–pink solid); ν_{max} (KBr): 3163, 3097, 3050, 3000, 2887, 1658, 1617, 1557, 1432, 1392, 1236, 1149, 869, 826, 816, 767, 583, 500 cm^{-1}; δ_H (DMSO-d_6): 13.23 (br s, 1H, NH), 9.82 (br dd, *J*=8.4, ~1.1 Hz, 1H, H-10), 9.76 (d, *J*≅0.8 Hz, 1H, H-6), 8.57 (s, 1H, H-4), 8.41 (br d, *J*≅8.0 Hz, 1H, H-7), 8.12 (ddd, *J*=8.4, 7.1, ~1.3 Hz, 1H, H-9), 7.99 (ddd, *J*=8.0, 7.1, ~1.1 Hz, 1H, H-8); δ_C (DMSO-d_6): 161.2, 159.7, 143.5, 139.4, 133.3, 131.2, 129.6, 129.0, 128.3, 126.2, 117.5; LRMS (ESI): 198.1; HRMS (ESI) for $C_{11}H_8N_3O$ $[M+H]^+$ found: 198.0672 calcd: 198.0667.

Acknowledgements

Funding by OTKA 33105, 31910, ETT 187/2000 and RAFO RUCA is gratefully acknowledged. Dr B. Maes thanks the Fund for Scientific Research (FWO-Vlaanderen) for an appointment as post-doctoral fellow. The authors wish to thank Professor Dr E. Esmans and Professor Dr F. Lemière for the use of their MS facilities, Professor Dr R. Dommisse for the use of his NMR facilities, Dr O. Egyed for NMR assignments, and Ing. J. Aerts, J. Schrooten, Ing. W. Van Dongen, V. Van Heurck and Ing. J. Verreydt for technical assistance.

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