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Pd-catalyzed intramolecular direct arylations at high temperature

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Abstract

Pd-catalyzed cyclodehydrohalogenation involving oxidative addition of aromatic C–Br or activated azaheteroaromatic C–Cl bonds and C(sp^2)–H activation have been investigated at high reaction temperatures (180–200 °C). This allowed the fast (10–30 min) synthesis of a variety of azaheteroaromatic ring systems (dibenzo[*f*,*h*]phthalazine, dibenzo[*f*,*h*]cinnoline, benzofuro[2,3-*d*]pyridazine, 5*H*-pyridazino[4,5-*b*]-indole, 7*H*-indolo[2,3-*c*]quinoline and 5*H*-δ-carboline) in moderate to good yields.

Keywords: Palladium; C(sp^2)–H activation; Microwave; Pyridazinone; Quinolinone; 5*H*-δ-Carboline

1. Introduction

Recently, we reported on the construction of D-ring substituted 7*H*-indolo[2,3-*c*]quinolines via regioselective Pd-catalyzed intramolecular direct arylation of *N*-(2-bromophenyl)quinolin-3-amines.[1] The cyclizations were achieved using a Pd-catalyst and involve C(sp^2)–H bond activation of a quinolinyl group. In our test system *N*-(2-bromophenyl)quinolin-3-amine, we observed that a very high loading of catalyst (23 mol %) and a long reaction time (48 h) were required to achieve a good conversion (and yield) at 130 °C [standard reaction conditions: 23 mol % $PdCl_2(PPh_3)_2$ and $NaOAc \cdot 3H_2O$ in DMA at 130 °C (oil bath temperature)]. A detailed study of the cyclization of *N*-(2-bromophenyl)quinolin-3-amine with an HPLC–UV system revealed that most of the conversion of starting material occurs in the first hour and subsequently a very slow further transformation to reaction product follows. Also when a lower catalyst loading was used a similar behaviour could be observed. Interestingly, when the reaction temperature was increased to 160 °C for the experiment with a 23 mol % catalyst loading an almost complete conversion occurred within one hour. This observation inspired us to study Pd-catalyzed intramolecular direct arylations at even higher temperatures. Microwave irradiation in a single-mode microwave unit (Discover, CEM) was selected to easily reach and monitor the high temperatures. In the meantime also the team of Bedford reported on the beneficial effect of high temperature in Pd-catalyzed intramolecular arylation reactions.[2] The reactions in the microwave were executed on the same scale as the oil bath experiments, only the concentration was increased by a factor of ten since the standard disposable microwave vials have only a volume of 10 mL. At 180 °C, using a loading of 23 mol %, a complete conversion of starting material could be achieved within only 10 min irradiation (ramp time included). When we determined the minimum amount of catalyst required to achieve full conversion of *N*-(2-bromophenyl)quinolin-3-amine in a 10 min reaction at 180 °C we found that 0.2 mol % is still sufficient. This is a reduction in reaction time by a factor 288 and a 115-fold decrease of the catalyst loading for the synthesis of 7*H*-indolo[2,3-*c*]quinoline. It seems that higher reaction temperatures increase conversion rate to a much larger extend than the catalyst decomposition rate. Working up the reaction mixture revealed that also the isolated yield was

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better than achieved under our standard (lower temperature) reaction conditions. This is most probably a combination of two factors: (a) in an oil bath at 130 °C using 23 mol % of catalyst the reaction can never be brought to complete conversion (even after 48 h of heating) and (b) the very high loading of catalyst generates a large amount of triphenylphosphine and triphenylphosphine oxide, which makes the work-up more difficult with reaction product loss as an obvious consequence. An exact comparison of oil bath and microwave heating revealed that no microwave effects have to be taken into account to explain the observed rate enhancements. The microwave-assisted ring closure of *N*-(2-bromophenyl)quinolin-3-amine is only governed by thermal effects (Arrhenius) and no microwave is therefore required to perform the reaction. Nevertheless, from a practical point of view, the microwave unit is still more convenient than classical heating since it is easier to reach, maintain and monitor the required high temperatures. The developed high temperature protocol proved to be general for the synthesis of substituted (Me, Cl, CF_3) 7*H*-indolo[2,3-*c*]-quinolines from the corresponding *N*-(2-bromophenyl)quinolin-3-amines. For these reactions the minimum amount of catalyst required was not determined and we always used a 1 mol % catalyst loading. In order to see whether the developed reaction conditions at high temperature can also be used to prepare other ring systems we decided to restudy some Pd-catalyzed ring closure reactions involving C(sp^2)–H activation we previously performed, in the frame of a collaboration with Hungarian scientists centered around the synthesis of pyridazino-fused ring systems,[3] under standard oil bath conditions using a high catalyst loading. In addition, two new substrate types were tested. In this way the general applicability of the high temperature protocol could be tested.

2. Results and discussion

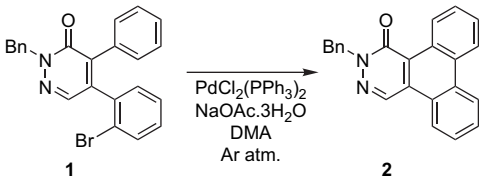
2.1. Six-membered ring formation

2.1.1. Synthesis of pyridazino-fused phenanthrenes

The synthesis of polycyclic aromatic carbons via metal-catalyzed direct arylation reactions is well documented in the literature.[4] In 2003 we explored if a similar approach could be used to prepare polycyclic aromatic carbons containing a pyridazine unit such as pyridazino-fused phenanthrenes.[5] For this purpose molecules with a phenyl and 2-bromophenyl group 'linked' via a pyridazine unit were synthesized.

Pd-catalyzed intramolecular arylation of 2-benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one (**1**) using 20 mol % $PdCl_2(PPh_3)_2$ and NaOAc·$3H_2O$ in DMA at 130 °C (oil bath temperature) was very slow since after 16 h only 30% of 2-benzyldibenzo[*f*,*h*]phthalazin-1(2*H*)-one (**2**) as well as 39% of starting material could be isolated.[5] A complete conversion of substrate could even not be achieved after 64 h since we still recovered 10% **1** (Table 1). When we subjected **1** to our microwave protocol [1 mol % $PdCl_2(PPh_3)_2$, NaOAc·$3H_2O$, DMA, 180 °C (μW), 10 min] a full conversion of starting material was observed within 10 min. The isolated yield was slightly higher than under classical reaction conditions (Table 1).

Table 1



1 2

	Standard protocol (Δ)	High temperature protocol (μW)
Catalyst load (mol %)	20	1
Temperature (°C)	130	180
Time (hh:mm)	64:00	00:10
Yield (%)	56	69

Pd-catalyzed intramolecular direct arylation of 5-(2-bromophenyl)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**3**) using 20 mol % catalyst at 130 °C (oil bath temperature) for 8 h gave 46% 2-methyldibenzo[*f*,*h*]cinnolin-3(2*H*)-one (**4**) (Table 2).[5] When the high temperature protocol was applied complete conversion of **3** was achieved in 10 min. The isolated yield almost doubled, which is a direct consequence of the more easy purification due to the reduced catalyst loading (Table 2).

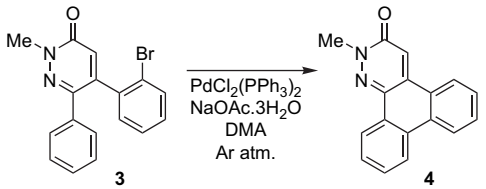
2.2. Five-membered ring formation

2.2.1. Synthesis of pyridazino-fused benzo[b]furane and indole

In 2004 we reported the first examples on catalytic C(4)–H activation of pyridazin-3(2*H*)-ones.[6] Pyridazin-3(2*H*)-ones 'tethered' via C-5 to a 2-bromophenyl ring via an oxygen and nitrogen atom could be cyclized via a Pd-catalyzed direct arylation. In this way benzofuro[2,3-*d*]pyridazine and 5*H*-pyridazino[4,5-*b*]indole ring systems were constructed.

Cyclization of 5-(2-bromophenoxy)-2-methylpyridazin-3(2*H*)-one (**5a**) using 20 mol % $PdCl_2(PPh_3)_2$ at 130 °C (oil bath temperature) for 6 h yielded 99% 2-methylbenzo[*b*]-furo[2,3-*d*]pyridazin-1(2*H*)-one (**6a**) (Table 3).[6] Under high temperature conditions with 1 mol % catalyst a slightly reduced yield of 85% was obtained but only a 10 min reaction time was required (Table 3). For the phenyl substituted

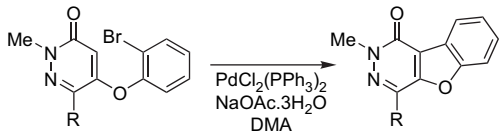
Table 2



3 4

	Standard protocol (Δ)	High temperature protocol (μW)
Catalyst load (mol %)	20	1
Temperature (°C)	130	180
Time (hh:mm)	08:00	00:10
Yield (%)	46	90

Table 3



	Standard protocol (Δ)	High temperature protocol (μW)
R=H		
Catalyst load (mol %)	20	1
Temperature (°C)	130	180
Time (hh:mm)	06:00	00:10
Yield (%)	99	85
R=Ph		
Catalyst load (mol %)	20	1
Temperature (°C)	130	180
Time (hh:mm)	11:00	00:30
Yield (%)	49	94

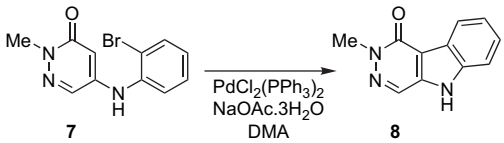
derivative, oil bath conditions with 20 mol % catalyst gave complete conversion in 11 h (Table 3).[6] Interestingly, ring closure of 5-(2-bromophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**5b**) under microwave irradiation with a 1 mol % catalyst loading could not be achieved in 10 min. A longer reaction time (30 min) at 180 °C was required for this substrate in order to convert all starting material. The obtained yield is substantially higher for the experiment performed under high reaction temperature conditions (Table 3). Also in this case this can be attributed to the work-up.

The aza-β-carboline derivative 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indole-1-one (**8**) has been previously synthesized by us in 73% yield via Pd-catalyzed intramolecular direct arylation of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (**7**) using 20 mol % catalyst (Table 4).[6] When our microwave protocol was applied, 85% of **8** could be obtained, albeit also in this case a 30 min reaction time was required (Table 4).

Due to the interest in the 5*H*-pyridazino[4,5-*b*]indole skeleton from a pharmaceutical point of view we decided to prepare some substituted derivatives using our high temperature protocol.[7] Therefore substituted 5-[(2-bromophenyl)amino]-pyridazin-3(2*H*)-ones were required, which we prepared via chemoselective Pd-catalyzed amination of 2-benzyl-5-iodopyridazin-3(2*H*)-one (**9**) with 2-bromoanilines (**10a**,**b**). 2-Benzyl- instead of 2-methyl-5-iodopyridazin-3(2*H*)-one was selected as substrate as this would allow a further derivatization of the cyclic hydrazide after ring system construction via debenzylation with $AlCl_3$. For 5-[(2-bromo-4-methylphenyl)amino]-pyridazin-3(2*H*)-one (**11b**) a good yield was obtained using $Pd(OAc)_2$/rac. BINAP in combination with 3 equiv K_2CO_3 in toluene (Table 5). However, Buchwald–Hartwig reaction of 2-benzyl-5-iodopyridazin-3(2*H*)-one with 2-bromo-4-trifluoromethoxyaniline did not yield a full conversion in the same reaction time. Switching to Cs_2CO_3, which is a stronger base in toluene, did afford 100% conversion and an isolated yield of 66% of 5-{[2-bromo-4-(trifluoromethoxy)phenyl]amino}pyridazin-3(2*H*)-one (**11a**) (Table 5).

While ring closure of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (**7**) at 180 °C required 30 min reaction time, cyclizations of 2-benzyl-5-{[2-bromo-4-(trifluoromethoxy)phenyl]amino}pyridazin-3(2*H*)-one (**11a**) and 2-benzyl-5-[(2-bromo-4-methylphenyl)amino]pyridazin-3(2*H*)-one (**11b**) could be achieved in 10 min (Table 6). The isolated yields were good in both cases.

Table 4

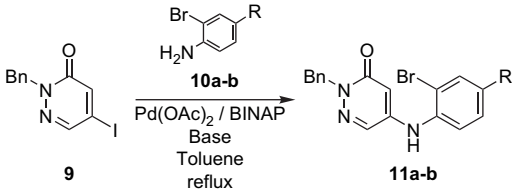


	Standard protocol (Δ)	High temperature protocol (μW)
Catalyst load (mol %)	20	1
Temperature (°C)	130	180
Time (hh:mm)	03:00	00:30
Yield (%)	73	85

2.2.2. Synthesis of indolo-fused quinoline

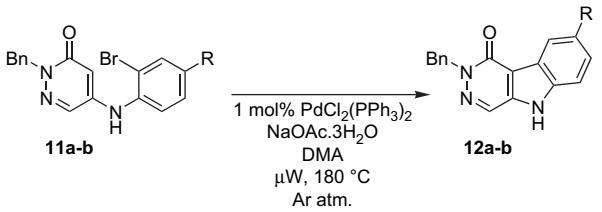
In the last five years Maes and co-workers have been involved in the validation of cryptolepines as potential new antiplasmodial drugs.[1,8] In the frame of this project, substituted derivatives of isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]-quinoline), the benzo-β-carboline isomer of the isomeric natural products cryptolepine, neocryptolepine and isocryptolepine, were required. 5-Methyl-5,7-dihydro-6*H*-indolo[2,3-*c*]quinolin-6-one (**16**) (formally a 5-methyl-5*H*-indolo[2,3-*c*]quinolin-6-ol) could be synthesized via our high temperature protocol. Complete conversion of 3-[(2-bromophenyl)amino]-1-methylquinolin-2(1*H*)-one (**15**) was smoothly achieved with 1 mol % of $PdCl_2(PPh_3)_2$ when 200 °C and a reaction time of 15 min were selected (Scheme 1). The observed C–H activation is rather interesting as it, to the best of our knowledge, represents the first example in which a C(4)–H of a quinolin-2(1*H*)-one unit is involved. One example dealing with a related C(4)–H activation in a pyridin-2(1*H*)-one has been reported by Padwa.[9]

Table 5



Compound	R	Base	Yield (%)
11a	OCF_3	Cs_2CO_3	66
11b	Me	K_2CO_3	61

Table 6



Compound	R	Time (hh:mm)	Yield (%)
12a	OCF_3	00:10	67
12b	Me	00:10	77

C(6)–H metal-catalyzed activation of pyridin-2(1*H*)-ones have been well studied.[10]

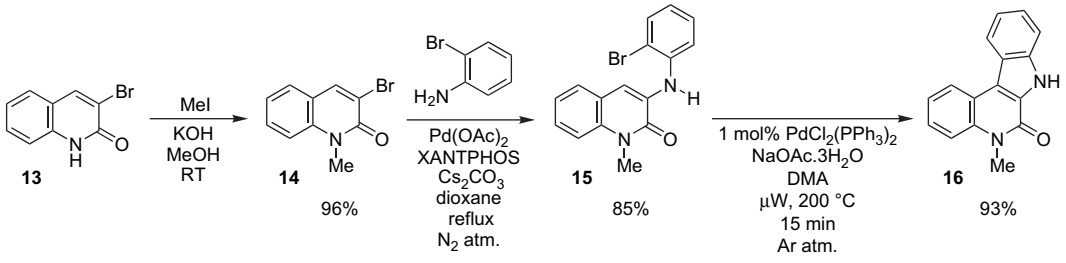
The substrate for the Pd-catalyzed intramolecular direct arylation was synthesized via site-selective Pd-catalyzed amination involving a chemoselective oxidative addition (Scheme 1).[11] Clearly, the C–Br bond of 3-bromo-1-methylquinolin-2(1*H*)-one (**14**) is more reactive than the C–Br bond of 2-bromoaniline due to the amino substituent of the latter, which sterically and electronically deactivates this bond for oxidative addition. 3-Bromo-1-methylquinolin-1(2*H*)-one (**14**) was easily obtained via methylation of 3-bromoquinolin-1(2*H*)-one (**13**) (Scheme 1). The synthesis of 3-bromoquinolin-1(2*H*)-one (**13**) has been previously reported by Erickson and co-workers.[12]

2.2.3. Synthesis of 5H-δ-carbolines (5H-pyrido[3,2-b]-indoles)

In 1999 Sakamoto and co-workers reported the synthesis of 5*H*-δ-carboline via Pd-catalyzed intramolecular arylation of 2-bromo-*N*-phenylpyridin-3-amine.[13] Although 5*H*-pyrido-[3,2-*b*]indole could be isolated in a moderate yield (51%), the published protocol is rather harsh since it required a reaction time of 67 h at 153 °C using a catalyst loading of almost 10 mol %. It is unclear if substituted derivatives can be prepared since no examples were shown in the paper. In 2002 Maes and co-workers reported on the chemoselective Pd-catalyzed amination of 2-chloro-3-iodopyridine with anilines.[14] *N*-Aryl-2-chloropyridin-3-amines could be selectively obtained in high yields. We wondered whether these pyridines could be used as substrates in a Pd-catalyzed cyclization involving catalytic aromatic C–H activation. The presence of a C(2)–Cl bond in the pyridine ring certainly poses a challenge due to the well known decreased reactivity of C–Cl in comparison with C–Br bonds in oxidative addition reactions. 2-Chloro-*N*-(4-methylphenyl)pyridin-3-amine (**17a**) was selected as test system. When our high temperature protocol was applied we observed transformation into 8-methyl-5*H*-pyrido[3,2-*b*]indole (**18a**). A catalyst loading of 1 mol % and 10 min reaction time at 180 °C were clearly not sufficient to achieve full conversion. Based on the commercial availability of 2-chloro-3-iodopyridine and a wide variety of anilines, we reasoned that an optimized protocol could be very useful for rapid 5*H*-δ-carboline library design. Therefore we searched for the minimum loading of catalyst required to get 100% conversion in 10 min, rather than performing attempts to increase the reaction time to achieve this goal. A systematic increase revealed that 8 mol % is required (Table 7). With these optimized reaction conditions, an isolated yield of 80% of **18a** was obtained. Unsubstituted 5*H*-δ-carboline (**18b**) could be made in 69% using this procedure. In comparison with the procedure of Sakamoto the obtained yield is almost 20% higher (Table 7) using a catalyst loading, which is still 1.75 mol % lower. Interestingly, the required reaction time to synthesize **18b** could be reduced by a factor 402 in comparison with the literature protocol. Next, we tried to introduce other substituents with different electronic properties on the phenyl ring involved in the aromatic C–H activation. Electron donating (OMe) as well as electron withdrawing groups (COOEt) in the 4-position of the phenylamino ring were well tolerated yielding the corresponding 5*H*-δ-carbolines (**18c** and **18d**) in moderate to high yields (Table 7).

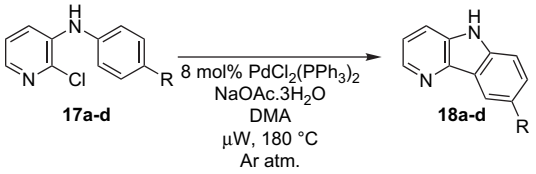
3. Conclusion

Pd-catalyzed cyclizations involving oxidative addition of an aromatic C–Br bond and C(sp^2)–H activation have been executed using $PdCl_2(PPh_3)_2$ as precatalyst with NaOAc·$3H_2O$ as base in DMA at 180 °C (μW). $PdCl_2(PPh_3)_2$ is a relatively cheap commercially available precursor for the in situ generation of Pd(0) species and could be used in a low loading only (1 mol %). Another attractive feature of the presented protocol is that the majority of the reactions can be performed in a reaction time of only 10 min. Only in a few cases the standard high temperature procedure was not sufficient. Via the selection of an even higher reaction temperature (200 °C) and/or longer reaction time (max. 30 min) full conversion could easily be achieved in these cases. Another



Scheme 1.

Table 7



Compound	R	Time (hh:mm)	Yield (%)
18a	Me	00:10	80
18b	H	00:10	69
18c	OMe	00:10	63
18d	COOEt	00:10	92

very attractive feature of the procedure is that Pd-catalyzed cyclizations involving oxidative addition of an activated azaheteroaromatic C–Cl bond and C(sp^2)–H activation could also be performed under similar reaction conditions albeit a higher loading of precatalyst was required to achieve full conversion in 10 min reaction time. The high temperature protocol presented seems to be generally applicable when aromatic C–Br or activated azaheteroaromatic C–Cl bonds are involved in the cyclizations and will be useful for the construction of other heteroaromatic ring systems. The short reaction times required, the high conversions and good yields make the procedure especially interesting for fast library design in medicinal and agrochemical research programmes.

4. Experimental

4.1. General

All melting points were determined on a Büchi apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer Avance 400 in the solvent indicated with TMS as the internal standard. The ^{1}H and ^{13}C NMR spectra of compound **11a**, **11b**, **12a**, **12b** were recorded on a Varian Mercury Plus spectrometer at 400 MHz (^{13}C NMR at 100 MHz) in the solvent indicated with TMS as the internal standard. All coupling constants are given in hertz and chemical shifts are given in parts per million. Flash column chromatography was performed on Kieselgel 60 (ROCC or Merck, 0.040–0.063 mm), for compounds **11a** and **11b** a Flash Master II Argonaut type apparatus was used (Kieselgel 60, Merck, 0.040–0.063 mm). The elemental analyses have been carried out with an Elementar Vario EL III apparatus.

4.2. General procedure for the high temperature Pd-catalyzed intramolecular direct arylations

Preparation of the stock solution of catalyst: $PdCl_2(PPh_3)_2$ (0.211 g, 0.03 mmol) was dissolved in 5 mL of DMA. Next, the mixture was flushed with Ar for 5 min and subsequently stirred until the catalyst was completely dissolved.

Procedure: A microwave vial of 10 mL was charged with pyridazin-3(2*H*)-one derivative (0.6 mmol) and $NaOAc\cdot 3H_2O$ (0.200 g, 1.47 mmol). Subsequently, the vial was flushed with argon for 1 min. Then, 1 mL of a stock solution of the catalyst in DMA (1 mol %) was added via a syringe and the resulting mixture was stirred and flushed with argon for an additional 2 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at 180 °C in a CEM Discover microwave apparatus. The set power was 100 W and the total heating time was 10 min (ramp time included). The reaction vial was cooled down to room temperature using a propelled air flow. It was evaporated to dryness under reduced pressure.

*4.2.1. 2-Benzyldibenzo[f,h]phtalazin-1(2H)-one (**2**)*

2-Benzyl-5-(2-bromophenyl)-4-phenylpyridazin-3(2*H*)-one (**1**)[5] (0.250 g, 0.60 mmol) was used as starting compound. The crude product was taken up in a mixture of water (30 mL) and dichloromethane (30 mL), the two layers were separated and the water phase was extracted with dichloromethane (30 mL). The combined organic layer was dried over $MgSO_4$, then evaporated yielding yellow crystals. It was purified with flash column chromatography on silica gel using toluene as the eluent yielding the title compound in 69%. The characterization data are identical as those reported in the literature.[5]

*4.2.2. 2-Methyldibenzo[f,h]cinnolin-3(2H)-one (**4**)*

5-(2-Bromophenyl)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**3**)[5] (0.204 g, 0.60 mmol) was used as starting compound. The crude product was taken up in a mixture of water (30 mL) and dichloromethane (30 mL), the two layers were separated and the water phase was extracted with dichloromethane (2×30 mL). The combined organic layer was dried over $MgSO_4$ and then evaporated. The residue was purified with flash column chromatography on silica gel using dichloromethane/ethyl acetate (7:3) as the eluent yielding the title compound in 90%. The characterization data are identical as those reported in the literature.[5]

*4.2.3. 2-Methylbenzo[b]furo[2,3-d]pyridazin-1(2H)-one (**6a**)*

5-(2-Bromophenoxy)-2-methylpyridazin-3(2*H*)-one (**5a**)[6] (0.169 g, 0.60 mmol) was used as starting compound. The crude product was taken up in a mixture of water (30 mL) and dichloromethane (30 mL), the two layers were separated and the water phase was extracted with dichloromethane (2×30 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified with flash column chromatography on silica gel using a 8:2 mixture of toluene/ethyl acetate as the eluent, yielding the title compound in 85%. The characterization data are identical as those reported in the literature.[6]

*4.2.4. 2-Methyl-4-phenylbenzo[b]furo[2,3-d]pyridazin-1(2H)-one (**6b**)*

5-(2-Bromophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**5b**)[6] (0.214 g, 0.60 mmol) was used as starting compound. In this case, the total heating time was 30 min. The crude product was taken up in a mixture of water (30 mL) and dichloromethane (30 mL), the two layers were separated

and the water phase was extracted with dichloromethane (2×30 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified with flash column chromatography on silica gel using a 3:2 mixture of heptane/ethyl acetate as the eluent, yielding the title compound in 94%. The characterization data are identical as those reported in the literature.[6]

4.2.5. 2-Methyl-2,5-dihydro-1H-pyridazino[4,5-b]indole-1-one (8)

5-[(2-Bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (**7**)[6] (0.168 g, 0.60 mmol) was used as starting compound. In this case, the total heating time was 30 min. The crude product was taken up in a mixture of water (30 mL) and dichloromethane (30 mL), the two layers were separated and the water phase was extracted with dichloromethane (2×30 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified with flash column chromatography on silica gel using a 9:1 mixture of ethyl acetate/chloroform as the eluent, yielding the title compound in 85%. The characterization data are identical as those reported in the literature.[6]

4.2.6. 2-Benzyl-8-(trifluoromethoxy)-2,5-dihydro-1H-pyridazino[4,5-b]indol-1-one (12a)

The general procedure was followed using 2-benzyl-5-{[2-bromo-4-(trifluoromethoxy)phenyl]amino}pyridazin-3(2*H*)-one (**11a**) (0.2640 mg, 0.6 mmol). The crude product was crystallized from a mixture of ethanol and water (9:1, 10 mL), then it was purified via flash column chromatography using hexane/ethylacetate (1:1) as the eluent yielding the title compound in 67%. White crystals; mp 267.1–269.7 °C; δ_H (DMSO-d_6): 12.55 (br s, 1H, NH), 8.50 (s, 1H, H-4), 8.10 (s, 1H, H-9), 7.34 (d, J=8.8 Hz, 1H, H-7), 7.50–7.45 (m, 1H, H-6), 7.35–7.20 (m, 5H, H-2″, 6″), 5.40 (s, 2H, 2-CH_2); δ_C (DMSO-d_6): 157.8, 143.2, 137.8, 137.7, 136.8, 128.4, 127.8, 127.7, 122.4, 121.1 (q, $^1J_{C-F}$=254 Hz), 120.1, 119.0, 114.3, 113.2, 111.4, 53.0; δ_F (DMSO-d_6): −57.49. Anal. Calcd for $C_{18}H_{12}F_3N_3O_2$: C, 60.17; H, 3.37; N, 11.69. Found: C, 60.28; H, 3.08; N, 11.51.

4.2.7. 2-Benzyl-8-methyl-2,5-dihydro-1H-pyridazino[4,5-b]-indol-1-one (12b)

The general procedure was followed using 2-benzyl-5-[(2-bromo-4-methylphenyl)amino]pyridazin-3(2*H*)-one (**11b**) (0.2220 mg, 0.6 mmol). The crude product was taken up in a mixture of water (40 mL) and dichloromethane (50 mL), the two layers were separated and the water phase was extracted with dichloromethane (30 mL). The combined organic layer was dried over $MgSO_4$, then evaporated yielding beige crystals. The residue was purified via flash column chromatography on silica gel (it was brought on column mixed with silica gel) using hexane/ethylacetate (1:1) as the eluent yielding the title compound in 77%. White crystals; mp 263.0–265.1 °C; δ_H (DMSO-d_6): 12.18 (br s, 1H, NH), 8.42 (s, 1H, H-4), 7.99 (s, 1H, H-9), 7.55 (d, J=8.4 Hz, 1H, H-7), 7.40–7.20 (m, 6H, H-2″-6″ and H-6), 5.41 (s, 2H, 2-CH_2), 2.51 (s, 3H, CH_3); δ_C (DMSO-d_6): 158.8, 138.7, 137.4, 137.2, 131.4, 129.1, 128.7, 128.5, 127.9, 123.2, 121.9, 113.1, 111.8, 53.7, 21.9. Anal. Calcd for $C_{18}H_{15}N_3O\cdot 0.2H_2O$: C, 73.80; H, 5.30; N, 14.34. Found: C, 73.86; H, 5.12; N, 13.87.

4.2.8. 5-Methyl-7H-indolo[2,3-c]quinolin-6(5H)-one (16)

The general procedure was followed using 3-(2-bromophenylamino)-1-methylquinolin-2(1*H*)-one (**15**) (0.197 g, 0.6 mmol) at 200 °C for 15 min; eluent: dichloromethane/methanol (96:4); yield: 93%; beige solid; mp >300 °C (decomp.); δ_H (DMSO-d_6): 12.34 (br s, 1H, NH), 8.53 (dd, J=7.8, 1.5 Hz, 1H, H-11), 8.49 (d, J=8.2 Hz, 1H, H-1), 7.69 (dd, J=8.5, 1.0 Hz, 1H, H-8), 7.65 (ddd, J=8.3, 0.9, 0.9 Hz, 1H, H-4), 7.54 (ddd, J=8.5, 7.1, 1.5 Hz, 1H, H-9), 7.48 (ddd, J=8.2, 7.1, 1.1 Hz, 1H, H-3), 7.44 (ddd, J=7.9, 7.1, 1.0 Hz, 1H, H-10), 7.32 (ddd, J=8.1, 7.0, 1.1 Hz, 1H, H-2), 3.84 (s, 3H, CH_3); δ_C (DMSO-d_6): 155.8, 139.5, 136.4, 127.6, 126.8, 126.2, 124.0, 123.1, 122.9, 122.6, 121.2, 119.4, 117.5, 116.1, 113.6, 29.7. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 76.83; H, 4.68; N, 11.21.

4.3. General procedure for the Pd-catalyzed amination reaction of 2-benzyl-5-iodopyridazin-3(2H)-one with 2-bromoaniline derivatives

A round-bottomed flask was purged with Ar and charged with $Pd(OAc)_2$ (0.03 mmol), racemic BINAP (0.03 mmol) and toluene (5 mL). While stirring, the mixture was flushed with Ar for approximately 10 min. Then, 2-benzyl-5-iodopyridazin-3(2*H*)-one (**9**) (1.5 mmol), 2-bromoaniline derivative (1.2 equiv), K_2CO_3 (3 equiv) (Cs_2CO_3 for the trifluoromethoxy derivative) and 5 mL toluene were added to the mixture. The resulting mixture was flushed with Ar for a few minutes under magnetic stirring and subsequently heated in an oil bath (oil bath temperature 120 °C, Ar atmosphere) for 24 h. The reaction mixture was filtered over Celite and rinsed well with dichloromethane (200 mL). The solvent was evaporated in vacuo and the residue was purified via flash column chromatography (Flash Master) using ethylacetate/hexane (1:1) mixture as the eluent.

4.3.1. 2-Benzyl-5-{[2-bromo-4-(trifluoromethoxy)phenyl]-amino}pyridazin-3(2H)-one (11a)

The general procedure was followed using 2-bromo-4-(trifluoromethoxy)aniline (0.4690 g, 1.8 mmol). Yield: 66%; beige crystals; mp 175.2–175.9 °C; δ_H ($CDCl_3$): 7.57 (d, J=2.7 Hz, 1H, H-6), 7.53–7.52 (m, 1H, H-3′), 7.42–7.38 (m, 3H, H-3″, 4″, 5″), 7.35–7.23 (m, 3H, H-2″, 6″ and H-6′), 7.20–7.15 (m, 1H, H-5′), 6.20 (d, J=2.7 Hz, 1H, H-4), 6.19 (br s, 1H, NH), 5.27 (s, 2H, 2-CH_2); δ_C ($CDCl_3$): 161.8, 146.5, 145.3, 137.3, 136.0, 131.7, 129.3, 128.5, 126.9, 124.4, 121.9, 120.6 (q, $^1J_{C-F}$=258 Hz), 118.3, 103.3, 54.9; δ_F ($CDCl_3$): −58.63. Anal. Calcd for $C_{18}H_{13}BrF_3N_3O_2$: C, 49.11; H, 2.98; N, 9.55. Found: C, 49.52; H, 2.75; N, 9.48.

4.3.2. 2-Benzyl-5-[(2-bromo-4-methylphenyl)amino]-pyridazin-3(2H)-one (**11b**)

The general procedure was followed using 2-bromo-4-methylaniline (0.3420 g, 1.8 mmol). Yield: 61%; beige crystals; mp 176.8–178.2 °C; δ_H ($CDCl_3$): 7.53 (d, J=2.7 Hz, 1H, H-6), 7.50–7.10 (m, 8H, aromatic protons), 6.15 (d, J=2.7 Hz, 1H, H-4), 6.05 (br s, 1H, NH), 5.26 (s, 2H, 2-CH_2), 2.33 (s, 3H, CH_3); δ_C ($CDCl_3$): 162.1, 145.9, 137.7, 137.5, 134.5, 134.1, 131.8, 129.9, 129.2, 128.4, 124.3, 118.4, 102.2, 54.8, 21.3. Anal. Calcd for $C_{18}H_{16}BrN_3O$: C, 58.39; H, 4.36; N, 11.35. Found: C, 58.33; H, 4.13; N, 11.19.

4.4. 3-Bromo-1-methylquinolin-2(1H)-one (**14**)

The synthesis of this compound has been reported previously.[15] We followed an alternative methylation procedure. A round-bottomed flask was charged with 3-bromoquinolin-2(1*H*)-one (**13**) (1.120 g, 5 mmol), KOH (0.421 g, 7.5 mmol) and methanol (10 mL). The mixture was flushed with N_2 under magnetic stirring. Subsequently, MeI (3.1 mL, 49.8 mmol) was added and the resulting mixture was stirred for 3 h at room temperature. Then the solvent was removed under reduced pressure. To the residue, H_2O (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (2×25 mL) and the combined organic phase was evaporated to dryness under reduced pressure yielding the target compound in 96%. White solid; mp 144 °C; δ_H ($CDCl_3$): 8.13 (s, 1H, H-4), 7.60 (ddd, J=8.8, 7.4, 1.6 Hz, 1H, H-6), 7.52 (dd, J=7.8, 1.4 Hz, 1H, H-8), 7.36 (d, J=8.6 Hz, 1H, H-5), 7.26 (ddd, J=7.9, 7.1, 0.8 Hz, 1H, H-7), 3.80 (s, 1H, CH_3); δ_C ($CDCl_3$): 158.5, 140.6, 139.4, 130.9, 128.1, 122.7, 120.6, 117.7, 114.4, 31.1.

4.5. 3-(2-Bromophenylamino)-1-methylquinolin-2(1H)-one (**15**)

A round-bottomed flask was charged with $Pd(OAc)_2$ (0.034 g, 0.150 mmol, 2.5 mol %) and XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) (0.096 g, 0.165 mmol, 5.5 mol %) followed by dry dioxane (12 mL) (freshly distilled). The mixture was flushed with N_2 for 10 min. Meanwhile, in another round-bottomed flask 3-bromo-1-methylquinolin-2(1*H*)-one (**14**) (0.708 g, 3 mmol), 2-bromoaniline (0.619 g, 3.6 mmol) and caesium carbonate (2.932 g, 9 mmol) (Aldrich, 99%) were weighed. To this mixture, the Pd-catalyst was added and the flask was flushed with N_2 for 5 min. The resulting mixture was stirred and heated at reflux (oil bath temperature: 110 °C) for 1 h under N_2 atmosphere. After cooling down to room temperature, dichloromethane (25 mL) was added and the suspension filtered over a path of Celite and rinsed well with dichloromethane (125 mL). The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using dichloromethane/heptane (6:4) as the eluent yielding the title compound in 87%. White solid; mp 108 °C; δ_H ($CDCl_3$): 7.63 (br s, 1H, NH), 7.63 (dd, J=8.0, 1.5 Hz, 1H, H-8), 7.56 (dd, J=8.1, 1.5 Hz, 1H, H-3′), 7.44 (dd, J=7.8, 1.4 Hz, 1H, H-5), 7.39 (ddd, J=8.4, 6.7, 1.5 Hz, 1H, H-7), 7.34 (ddd, J=8.5, 7.0, 1.2 Hz, 1H, H-4′), 7.34 (dd, J=8.5, 1.4 Hz, 1H, H-6′), 7.30 (s, 1H, H-4), 7.22 (ddd, J=8.0, 6.6, 1.2 Hz, 1H, H-6), 6.91 (ddd, J=8.4, 7.0, 1.1 Hz, 1H, H-5′), 3.86 (s, 3H, CH_3); δ_C ($CDCl_3$): 158.7, 138.9, 134.3, 133.5, 132.0, 128.1, 126.6, 126.4, 123.2, 122.9, 121.7, 119.5, 115.7, 113.9, 108.4, 30.4. Anal. Calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.34; H, 3.80; N, 8.53.

4.6. General procedure for the synthesis of 5H-δ-carbolines (**18**) via high temperature Pd-catalyzed intramolecular direct arylations

A microwave vial of 10 mL was charged with the appropriate *N*-aryl-2-chloropyridin-3-amine (**17**) (0.6 mmol), $PdCl_2(PPh_3)_2$ (0.0337 g, 0.048 mmol, 8 mol %) and $NaOAc\cdot 3H_2O$ (0.200 g, 1.47 mmol). Subsequently, the vial was flushed with Ar for 1 min. Then, 1 mL of DMA was added via a syringe and the resulting mixture was stirred and flushed with Ar for an additional 2 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at 180 °C in a CEM Discover microwave apparatus. The set power was 100 W and the total heating time was 10 min. After the reaction vial was cooled down to room temperature using a propelled air flow, it was opened and poured in a round-bottomed flask. The vial was rinsed with methanol (50 mL) and the combined organic phase was evaporated to dryness. Finally, the crude product was purified via column chromatography on silica gel (the residue was brought on column mixed with silica) yielding the title compound.

4.6.1. 8-Methyl-5H-pyrido[3,2-b]indole (**18a**)

The general procedure was followed using 2-chloro-*N*-(4-methylphenyl)pyridin-3-amine (**17a**)[14] (0.1312 g, 0.6 mmol); eluent: dichloromethane/ethyl acetate (95:5); yield: 80%; white solid; mp 212 °C; δ_H (DMSO-d_6): 11.27 (br s, 1H, N–H), 8.43 (dd, J=4.6, 1.4 Hz, 1H, H-2), 8.00 (d, J=1.7 Hz, 1H, H-9), 7.85 (dd, J=8.2, 1.4 Hz, 1H, H-4), 7.47 (d, J=8.3 Hz, 1H, H-6), 7.35 (dd, J=8.2, 4.6 Hz, 1H, H-3), 7.33 (dd, J=8.3, 1.7 Hz, 1H, H-7), 2.49 (s, 3H, CH_3); δ_C (DMSO-d_6): 141.0, 140.8, 138.8, 133.1, 128.7, 128.0, 121.7, 119.9, 119.6, 117.7, 111.3, 21.0. Anal. Calcd for $C_{12}H_{10}N_2\cdot 0.8H_2O$: C, 73.30; H, 5.95; N, 14.25. Found: C, 74.27; H, 5.11; N, 14.22.

4.6.2. 5H-Pyrido[3,2-b]indole (**18b**)

The general procedure was followed using 2-chloro-*N*-phenylpyridin-3-amine (**17b**)[14] (0.1228 g, 0.6 mmol); eluent: dichloromethane/ethyl acetate (9:1); yield: 69%. The characterization data are identical as those reported in the literature.[13,16]

4.6.3. 8-Methoxy-5H-pyrido[3,2-b]indole (**18c**)

The general procedure was followed using 2-chloro-*N*-(4-methoxyphenyl)pyridin-3-amine (**17c**)[14] (0.1408 g, 0.6 mmol); eluent: dichloromethane/ethyl acetate (8:2); yield: 63%; pale yellow solid; mp 155 °C; δ_H (DMSO-d_6): 11.22 (br s, 1H,

N–H), 8.43 (dd, J=4.6, 1.4 Hz, 1H, H-2), 7.85 (dd, J=8.2, 1.4 Hz, 1H, H-4), 7.69 (d, J=2.6 Hz, 1H, H-9), 7.49 (d, J=8.8 Hz, 1H, H-6), 7.36 (dd, J=8.2, 4.6 Hz, 1H, H-3), 7.16 (dd, J=8.8, 2.6 Hz, 1H, H-7), 3.88 (s, 3H, O–CH_3); δ_C (DMSO-d_6): 153.4, 141.0, 140.7, 135.3, 133.5, 121.8, 119.9, 117.9, 117.1, 112.5, 101.8, 55.5. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.45; H, 4.88; N, 14.07.

4.6.4. Ethyl 5H-pyrido[3,2-b]indole-8-carboxylate (**18d**)

The general procedure was followed using ethyl 4-[(2-chloropyridin-3-yl)amino]benzoate (**17d**)[14] (0.1660 g, 0.6 mmol); eluent: dichloromethane/ethyl acetate (8:2); yield: 92%; white solid; mp 220–221 °C; δ_H (DMSO-d_6): 11.89 (br s, 1H, N–H), 8.85 (d, J=1.7 Hz, 1H, H-9), 8.56 (dd, J=4.6, 1.4 Hz, 1H, H-2), 8.13 (dd, J=8.6, 1.7 Hz, 1H, H-7), 7.99 (dd, J=8.2, 1.4 Hz, 1H, H-4), 7.67 (d, J=8.6 Hz, 1H, H-6), 7.48 (dd, J=8.2, 4.6 Hz, 1H, H-3), 4.38 (q, 2H, O–CH_2), 1.39 (t, 3H, CH_3); δ_C (DMSO-d_6): 166.2, 143.0, 142.1, 140.9, 133.7, 128.2, 121.9, 121.2, 121.0, 120.9, 118.8, 111.7, 60.4, 14.2. Anal. Calcd for $C_{14}H_{12}N_2O_2 \cdot 1.1H_2O$: C, 64.65; H, 5.50; N, 10.77. Found: C, 64.90; H, 5.23; N, 10.74.

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