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A new, direct, and efficient synthesis of benzonaphthyridin-5-ones

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Abstract—Microwave-assisted Suzuki cross-coupling reaction of 2-fluorophenylboronic acid with all orthochlorocyanopyridine isomers allowed the rapid syntheses of key intermediates for anionic ring closure, which was performed using potassium hydroxide under microwave irradiation to give benzonaphthyridin-5-ones in high yields.

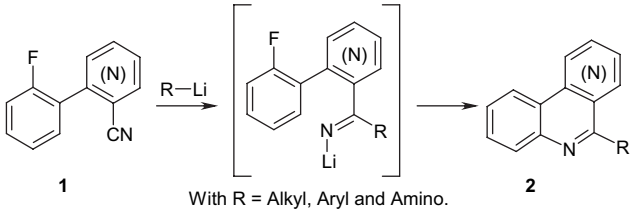
1. Introduction

Benzonaphthyridines are of great interest regarding to their diverse biological activities[1] and as 'aza-analogues' of phenanthridines, which have been widely studied in the field of medicinal chemistry.[2] However their syntheses are not scalable and suffer from a lack of diversity. To our point of view, benzonaphthyridin-5-ones could be useful scaffolds for the syntheses of diverse 5-substituted compounds. In this paper, we wish to report a new and an efficient two-step synthesis of the four benzonaphthyridin-5-one isomers **5a**–**d**. Three of them have already been reported generally with poor to low yield: 6*H*-benzo[*f*][1,7]naphthyridin-5-one **5a**,[3] 6*H*-benzo[*c*][2,7]naphthyridin-5-one **5b**,[3a,4] and 6*H*-benzo[*h*][1,6]naphthyridin-5-one **5c**.[3a,5] The synthesis of 6*H*-benzo[*c*][2,6]naphthyridin-5-one **5d** has not been reported yet.

2. Results and discussion

2.1. Strategy

We hypothesized that a two-step procedure including an anionic ring closure and Suzuki cross-coupling could lead directly to benzonaphthyridinone systems. This strategy was supported by the work of the Begtrup's team[6,7] who demonstrated that anionic ring closure could be a powerful method to synthesize 6-substituted phenanthridines and 5-substituted benzonaphthyridines **2** by the attack of a lithiated species on the nitrile function of biaryl **1** and subsequent intramolecular nucleophilic aromatic substitution of the fluorine atom (Scheme 1).



Scheme 1. Anionic ring closure.

However, the scope of this sequence was still limited to the variety of organometallic derivatives employed to achieve the second step: alkyllithium and lithium amide reagents mainly. In the benzonaphthyridine series, this reaction had only been reported using lithium morpholide as a nucleophile.[7] This is the reason why in order to enlarge the scope of this methodology we planned to prepare the lactam moieties using, this time, the hydroxide ion as the nucleophile.

Before considering the improvement of the anionic ring closure, it was necessary to have an easy access to biaryl systems bearing a cyano group in position 2 and a fluorine atom in position 2′. These biaryl structures could be obtained using the Suzuki–Miyaura cross-coupling reaction.[8] Meanwhile four different partnerships were possible to achieve the cross-coupling (Table 1). The pathway A using orthofluoropyridylboronic derivatives was not usable for two reasons. First these species, for which we described a synthesis,[9] remain very expensive. Second, no synthesis for a 4-fluoro-3-pyridylboronic or 3-fluoro-2-pyridylboronic species is available. The B pathway using orthofluorobenzene halides and orthocyanopyridylboronic acids or esters had already been reported by Hansen and co-workers.[7] But these orthocyanopyridylboronic species are quite unstable[10] and no 2-pyridyl derivative has been described yet. The pathway C was also limited (as pathways A and B) because of the

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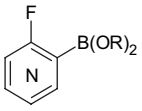
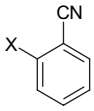
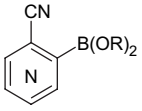
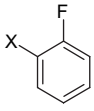
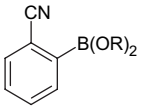
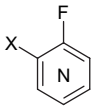
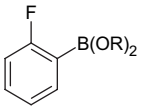
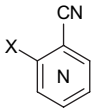
Table 1. Cross-coupling partnerships

Boronics	Halides	Cross-coupling partnerships
		A
		B
		C
		D

expensiveness of fluoropyridine derivatives and the instability of orthocyanophenylboronic species during the cross-coupling reaction.[11] The last partnership D consisted in fusing 2-fluorophenylboronic and orthochlorocyanopyridine **3**. Since we had described a general method for the ortholithiation of cyanopyridines[12] that permitted to synthesize all isomers of orthochlorocyanopyridine **3**, we first decided to apply this last strategy using commercial 2-fluorophenylboronic acid, which was able to furnish the four isomers of benzonaphthyridin-5-one **5a–d** in good conditions.

2.2. Cross-coupling reaction of orthochlorocyanopyridines with 2-fluorophenylboronic acid

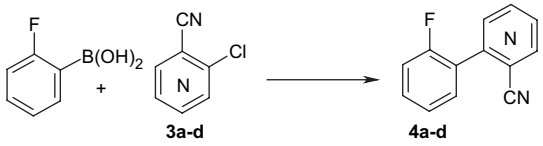
Our first attempt of cross-coupling at 100 °C in DMF with K_3PO_4 and $Pd(PPh_3)_4$ starting from **3b** was disappointing. However, using 2 equiv of 2-fluorophenylboronic acid in order to compensate the protodeboronation side reaction and increasing the reaction time from 24 to 36 h, we obtained a 80% yield. Finally, taking into account the recent results of several groups[13] who had demonstrated that the use of microwave energy could shorten the reaction time in this reaction, we conducted an assisted microwave reaction in a sealed tube. These latter conditions permitted the isolation of **4b** with a good 85% yield after 30 min at 150 °C (Table 2).

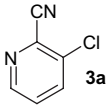
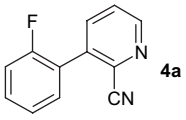
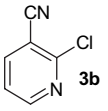
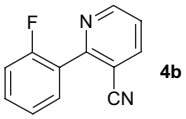
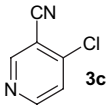
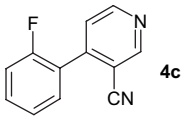
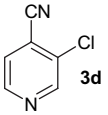
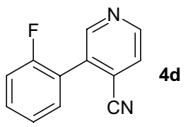
We then applied these reaction conditions to the isomers **3a** and **3d**, which gave **4a** and **4d** with 67 and 77% yield, respectively. In the case of **3c** it was necessary to avoid the side reaction of the chlorine atom in aromatic nucleophilic substitutions, we therefore replaced the K_3PO_4 by CsF to obtain **4c** with a 71% yield.

2.3. Anionic ring closure

To achieve the second step we first evaluated the feasibility of the anionic ring closure with KOH from 4-cyano-3-(2-fluorophenyl)pyridine **4d**. The first attempt with 5 equiv of KOH in refluxing methanol for 24 h only led to the carboxamide **6**. When the temperature was raised to 150 °C in a sealed tube for 1 h, the benzonaphthyridin-5-one **5d** was

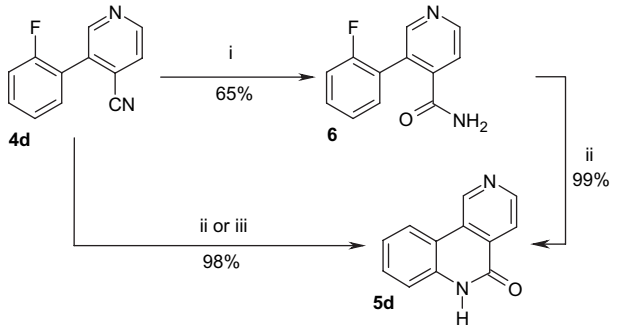
Table 2. Microwave-assisted cross-coupling reaction[a]



Starting materials	Products	Yields (%)[b]
 **3a**	 **4a**	67
 **3b**	 **4b**	85
 **3c**	 **4c**	71[c]
 **3d**	 **4d**	77

[a] Reaction conditions: 1 equiv of aromatic halide, 2 equiv of 2-fluorophenylboronic acid, 5% mol of $Pd(PPh_3)_4$, 2.5 equiv of K_3PO_4, DMF, 150 °C, microwave heating, sealed tube, 30 min.
[b] Isolated yields.
[c] CsF (2.5 equiv) was used instead of K_3PO_4.

obtained in 98% yield. The use of microwave heating conditions reduced the reaction time to 10 min maintaining the same yield (Scheme 2). We then tested the reactivity of the carboxamide **6** under our microwave conditions. Its total conversion into the benzonaphthyridin-5-one **5d** was observed, with no formation of the corresponding carboxylic acid. In the absence of KOH, the carboxamide **6** did not react and only the starting material was recovered. Therefore these experiments showed that the formation of an anion intermediate was needed to achieve the cyclization.



Scheme 2. Anionic ring closure using various temperatures under microwave or conventional heating conditions (isolated yields): (i) KOH 5 equiv, MeOH, reflux, conventional heating, 24 h, (ii) KOH 5 equiv, MeOH, 150 °C, conventional heating, sealed tube, 1 h, and (iii) KOH 5 equiv, MeOH, 150 °C, microwave heating, sealed tube, 10 min.

We further investigated this reaction regarding the quantity and the nature of the base employed (Table 3). With 1 equiv

Table 3. Microwave-assisted anionic ring closure varying nature and quantity of base[a]

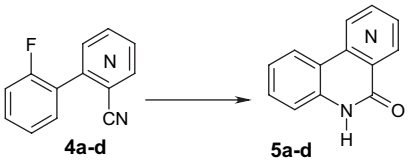
Bases	Equivalents	Reaction times (min) μW	Products molar ratio[b]		
			4d	**6**	**5d**
KOH	1	10	23	47	30
KOH	1	20	16	42	42
KOH	3	10	3	9	88
KOH	3	20	3	3	94
KOH	5	10	0	0	100
NaOH	5	10	4	1	95

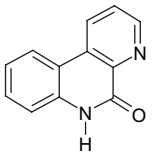
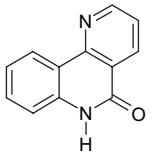
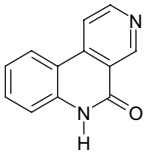
[a] Reaction conditions: MeOH, 150 °C, microwave heating, and sealed tube.
[b] Molar ratio determined by analysis of the crude ^{1}H NMR spectra.

of KOH, the reaction was not completed even after increasing the reaction time from 10 to 20 min. With 3 equiv of KOH the ratio of the benzonaphthyridin-5-one **5d** was increased, but the reaction was still not finished yet after 10 min. The same reaction conducted within 20 min did not allow a total conversion of **4d** into **5d**. The use of 5 equiv of KOH in a 10 min experiment showed us a total conversion of **4d** into **5d** without formation of **6**. The same reactive conditions conducted with NaOH appeared to be less efficient for this reaction. Finally, the best conditions to achieve the reaction were: 5 equiv of KOH, 150 °C, and 10 min under microwave heating.

Then, the three fluorophenylcyanopyridines **4a–c** were subjected to these best conditions to give the three corresponding benzonaphthyridin-5-ones **5a–c** in nearly quantitative yields (Table 4).

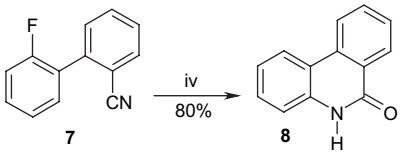
Table 4. Microwave-assisted anionic ring closure[a]



Starting materials	Products	Yields[b] (%)	Product number
4a		95	**5a**
4b		99	**5b**
4c		95	**5c**

[a] Reaction conditions: KOH 5 equiv, MeOH, 150 °C, microwave heating, sealed tube, 10 min.
[b] Isolated yields.

Because our methodology was not described in the corresponding phenanthridinic system our anionic ring closure was finally tested on the 2′-fluorobiphenyl-2-carbonitrile **7** (Scheme 3). The 5*H*-phenanthridin-6-one **8** was obtained in a good 80% yield but the reaction time has to be increased to 30 min. The π-deficient nature of the pyridine nucleus could explain the milder condition needed to achieve the transformation in benzonaphthyridin-5-one.



Scheme 3. Anionic ring closure using 2′-fluorobiphenyl-2-carbonitrile **7** (isolated yields): (iv) KOH 5 equiv, MeOH, 150 °C, microwave heating, sealed tube, 30 min.

3. Conclusion

In conclusion, we have developed a very efficient microwave-assisted synthesis of the benzonaphthyridin-5-ones **5a–d** in a two-step procedure involving Suzuki cross-coupling reaction followed by original KOH promoted anionic ring closure. The benzonaphthyridin-5-ones **5a–d** were obtained in 63–84% overall yields starting from **3a–d**. Both nitrile and carboxamide groups were reactive under these conditions and could allow an easy scalable access to benzonaphthyridine scaffolds with a potential interest in the field of medicinal chemistry. Finally, a new access to the 5*H*-phenanthridin-6-one enlarges the scope of our reaction to benzenic derivatives. Furthermore, we are currently exploring the use of our approach to synthesize aza-heterocyclic systems.

4. Experimental

4.1. General

All commercial reagents were used as received except THF, which was distilled from Na/benzophenone. Melting points were determined on a kofler melting point apparatus. IR spectra were recorded with a Perkin–Elmer BX FTIR. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz with a Jeol Lambda 400 NMR spectrometer. The microwave reactions were performed using a Biotage Initiator microwave oven. Temperatures were measured with an IR-sensor and the reactions are given as hold times.

4.2. General procedure for the synthesis of ortho-chlorocyanopyridines (3a, 3c, and 3d)

To a stirred solution under N_2 of 2,2,6,6-tetramethylpiperidine (20.2 mmol, 3.4 mL) in THF (40 mL) was added at −30 °C 2.5 M *n*-butyllithium (19.2 mmol, 7.7 mL). The solution was allowed to reach 0 °C, kept under stirring during 15 min and cooled to −80 °C. A solution of the chosen cyanopyridine (9.6 mmol, 1 g) in THF (20 mL) was slowly added to the mixture over 15 min. After stirring 30 min at −80 °C, a solution of hexachloroethane (20.2 mmol, 4.78 g) in THF (10 mL) was slowly added over 15 min and

the resulting mixture was stirred for 30 min. The solution was then allowed to warm slowly to room temperature. The mixture was quenched with 40 mL of a saturated NH_4Cl solution. The solution was extracted with EtOAc (3×100 mL), the combined organic layers were washed with brine (2×100 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The products were purified by silica gel chromatography using EtOAc/cyclohexane (1/4) as eluent.

4.2.1. 3-Chloropyridine-2-carbonitrile 3a. Starting from 2-cyanopyridine and following the general procedure, the product was obtained as a pale yellow powder (0.99 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51 (dd, ^3J=4.6 Hz, ^3J=8.5 Hz, 1H), 7.88 (dd, ^4J=1.4 Hz, ^3J=8.5 Hz, 1H), 8.63 (dd, ^4J=1.4 Hz, ^3J=4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=114.6, 127.5, 133.5, 135.9, 137.6, 148.7; IR (KBr) 3437, 3049, 2970, 2238 (CN), 1563, 1421, 1062, 1041, 813, 746, 676, 559, 507 cm^{-1}; mp 84 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22. Found: C, 52.39; H, 1.95; N, 19.98.

4.2.2. 4-Chloronicotinonitrile 3c. Starting from 3-cyanopyridine and following the general procedure, the product was obtained as a pale yellow powder (0.5 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51 (d, ^3J=5.3 Hz, 1H), 8.71 (d, ^3J=5.3 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=111.4, 113.8, 124.6, 146.5, 153.4, 153.8; IR (KBr) 3426, 3091, 2926, 2236 (CN), 1572, 1549, 1473, 1404, 1291, 1187, 1101, 844, 798, 728, 700, 571, 476 cm^{-1}; mp 86 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22. Found: C, 52.31; H, 2.07; N, 19.93.

4.2.3. 3-Chloroisonicotinonitrile 3d. Starting from 4-cyanopyridine and following the general procedure, the product was obtained as pale orange needles (0.99 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.56 (d, ^3J=4.8 Hz, 1H), 8.68 (d, ^3J=4.8 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=113.7, 120.9, 126.3, 133.1, 148.1, 150.4; IR (KBr) 3016, 2953, 2475, 2238 (CN), 1573, 1471, 1401, 1384, 1280, 1162, 1036, 840, 795, 708, 576 cm^{-1}; mp 80 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22. Found: C, 52.39; H, 2.37; N, 20.32. Lit.[14]

4.3. General procedure for the microwave Suzuki cross-coupling synthesis of 4a–d and 7

In a microwave vial with a magnetic stir bar was introduced K_3PO_4 (18 mmol, 3.8 g), 2-fluorophenylboronic acid (14 mmol, 2 g), and $Pd(PPh_3)_4$ (5%, 0.4 g). The vial was sealed and purged with argon through the septum inlet. A solution of orthochlorocyanopyridine **3a–d** (7 mmol, 1 g) in DMF (15 mL) was degassed with argon and added with a syringe through the vial's septum. The suspension was then heated at 150 °C under microwave irradiation for half an hour. The resulting mixture was poured into 100 mL of water and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The products were purified by silica gel chromatography using EtOAc/cyclohexane (1/4) as eluent.

4.3.1. 3-(2-Fluorophenyl)pyridine-2-carbonitrile 4a. Starting from **3a** and following the general procedure, the product was obtained as a white powder (0.96 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.23 (m, 1H), 7.31 (td, J=7.5 and 1.2 Hz, 1H), 7.43–7.55 (m, 2H), 7.60 (dd, ^3J=8.0 Hz, ^3J=4.6 Hz, 1H), 7.88 (dd, ^3J=8.0 Hz, ^4J=1.4 Hz, 1H), 8.73 (dd, ^3J=4.7 Hz, ^4J=1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.3 (d, J_{C-F}=22 Hz), 116.5, 123.1 (d, J_{C-F}=15 Hz), 124.8 (d, J_{C-F}=4 Hz), 126.4, 131.2 (d, J_{C-F}=2 Hz), 131.8 (d, J_{C-F}=8 Hz), 133.5, 136.6, 138.7 (d, J_{C-F}=2 Hz), 150.0, 159.5 (d, J_{C-F}=248 Hz); IR (KBr) 3066, 3050, 2236 (CN), 1835, 1615, 1579, 1496, 1457, 1416, 1217, 1111, 1001, 811, 775, 689, 551 cm^{-1}; mp 88 °C. Lit.[7]

4.3.2. 2-(2-Fluorophenyl)nicotinonitrile 4b. Starting from 2-chloro-3-cyanopyridine and following the general procedure, the product was obtained as a white powder (1.22 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.21 (m, 1H), 7.25 (td, J=7.5 and 1.1 Hz, 1H), 7.38 (dd, ^3J=4.8 Hz, ^3J=7.8 Hz, 1H), 7.41–7.47 (m, 1H), 7.52 (td, J=7.5 and 1.7 Hz, 1H), 8.02 (dd, ^3J=7.8 Hz, ^4J=1.7 Hz, 1H), 8.85 (dd, ^3J=4.8 Hz, ^4J=1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=110.4, 116.3 (d, J_{C-F}=21 Hz), 116.4, 122.1, 124.5 (d, J_{C-F}=4 Hz), 125.5 (d, J_{C-F}=14 Hz), 131.2 (d, J_{C-F}=2.5 Hz), 132.1 (d, J_{C-F}=8 Hz), 140.7, 152.6, 157.3, 159.7 (d, J_{C-F}=249 Hz); IR (KBr) 3066, 2226 (CN), 1613, 1577, 1556, 1493, 1459, 1433, 1219, 1110, 835, 809, 760, 687, 621, 552 cm^{-1}; mp 76 °C. Lit.[7]

4.3.3. 4-(2-Fluorophenyl)nicotinonitrile 4c. Starting from **3c** according to the general procedure and replacing K_3PO_4 by CsF (18 mmol, 2.73 g), the product was obtained as a white powder (1.01 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.32 (td, J=9.0 and 0.8 Hz, 1H), 7.32 (td, J=7.6 and 0.8 Hz, 1H), 7.45–7.55 (m, 3H), 8.86 (d, J=4.8 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=110.1, 115.9, 116.5 (J_{C-F}=21 Hz), 123.2 (J_{C-F}=13 Hz), 124.9 (J_{C-F}=4 Hz), 125.0, 130.6 (J_{C-F}=2 Hz), 132.2 (J_{C-F}=7 Hz), 147.1, 152.6, 153.5, 159.1 (J_{C-F}=249 Hz); IR (KBr), 3056, 2233 (CN), 1615, 1585, 1474, 1447, 1398, 1257, 1210, 1109, 1040, 846, 826, 775, 756, 620, 587, 551, 529; mp 101 °C. Lit.[7]

4.3.4. 3-(2-Fluorophenyl)isonicotinonitrile 4d. Starting from **3d** and following the general procedure, the product was obtained as a white powder (1.10 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.25–7.27 (m, 1H), 7.32 (td, J=7.5 and 1.1 Hz, 1H), 7.46 (td, J=7.5 and 1.8 Hz, 1H), 7.49–7.52 (m, 1H), 7.65 (d, ^3J=5.1 Hz, 1H), 8.80 (d, ^3J=5.1 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=115.7, 116.4 (d, J_{C-F}=22 Hz), 120.5, 122.3 (d, J_{C-F}=15 Hz), 124.7 (d, J_{C-F}=4 Hz), 125.6, 131.1 (d, J_{C-F}=2 Hz), 131.8 (d, J_{C-F}=8 Hz), 133.3, 149.4, 151.6 (d, J_{C-F}=2 Hz), 159.5 (d, J_{C-F}=248 Hz); IR (KBr) 3064, 2233 (CN), 1614, 1577, 1500, 1472, 1450, 1402, 1260, 1219, 1199, 1074, 841, 828, 785, 763, 752, 586, 555 cm^{-1}; mp 50 °C. Lit.[7]

4.3.5. 2′-Fluorobiphenyl-2-carbonitrile 7. Starting from 2-bromobenzonitrile and following the general procedure, the product was obtained as a white powder (0.92 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.19–7.30 (m, 2H), 7.40–7.52 (m, 4H), 7.66 (ddd, J=8.0, 7.3, and 1.3 Hz, 1H), 7.78 (ddd, J=7.6, 1.5, and 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=112.9, 116.2 (d, J_{C-F}=22 Hz), 118.1, 124.3 (d, J_{C-F}=4 Hz), 125.8 (d, J_{C-F}=14.8 Hz), 128.2, 130.8

(d, J_{C-F}=8 Hz), 131.0 (d, J_{C-F}=2.5 Hz), 131.2 (d, J_{C-F}=3.0 Hz), 132.5, 133.3, 139.6, 159.6 (J_{C-F}=248 Hz). Lit.[6a]

4.4. Synthesis of 3-(2-fluorophenyl)isonicotinamide 6

3-(2-Fluorophenyl)isonicotinonitrile **4d** (1 mmol, 0.2 g) and KOH (5 mmol, 0.28 g) were solubilized in MeOH (5 mL) in a sealed tube. The mixture was then heated at 65 °C for 24 h. The resulting solution was poured into 20 mL of water and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The crude product was purified by silica gel chromatography using CH_2Cl_2/EtOAc (1/1) and EtOAc as eluents to give 3-(2-fluorophenyl)isonicotinamide **6** as a yellow powder (0.14 g, 65%).^{1}H NMR (400 MHz, $CDCl_3$) δ=5.72 (br s, 1H), 5.98 (br s, 1H), 7.17 (t, J=8.5 Hz, 1H), 7.26 (t, J=7.6 Hz, 1H), 7.37–7.48 (m, 2H), 7.61 (d, ^3J=4.8 Hz, 1H), 8.63 (s, 1H), 8.71 (d, ^3J=4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.1 (d, J_{C-F}=21 Hz), 121.8, 124.0 (d, J_{C-F}=15 Hz), 124.8 (d, J_{C-F}=3 Hz), 128.4, 130.8 (d, J_{C-F}=8 Hz), 131.1 (d, J_{C-F}=15 Hz), 132.1 (d, J_{C-F}=10 Hz), 142.0, 149.8, 151.6, 159.7 (d, J_{C-F}=247 Hz), 168.5; IR (KBr) 3312 (NH), 3045, 1666 (CO), 1582, 1477, 1451, 1388, 1257, 1203, 1111, 1082, 849, 763, 625 cm^{-1}; mp 174 °C; HRMS/ESI (g mol^{-1}) Calcd for $C_{12}H_{10}FN_2O$ $[M+H]^+$ 217.0777; found 217.072.

4.5. General procedure for microwave anionic ring closure synthesis of 5a–d

A biaryl **4a–d** (2.4 mmol, 0.49 g) and KOH (12 mmol, 0.69 g) were solubilized in MeOH (7 mL) in a microwave vial. The suspension was then heated at 150 °C under microwave irradiation for 10 min. The resulting mixture was poured into 20 mL of water and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated to give analytically pure products **5a–d**.

4.5.1. 6*H*-Benzo[*f*][1,7]naphthyridin-5-one 5a. Starting from **4a** and following the general procedure, the product was obtained as a white powder (0.46 g, 95%). ^{1}H NMR (400 MHz, DMSO) δ=7.28 (td, J=7.3 and 1.2 Hz, 1H), 7.37 (dd, J=8.2 and 0.7 Hz, 1H), 7.52 (td, J=8.2 and 1.2 Hz, 1H), 7.83 (dd, ^3J=4.4 Hz, ^3J=8.3 Hz, 1H), 8.40 (d, J=7.3 Hz, 1H), 8.88 (dd, ^4J=1.5 Hz, ^3J=4.4 Hz, 1H), 8.95 (dd, ^4J=1.5 Hz, ^3J=8.3 Hz, 1H), 11.97 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.9, 116.5, 122.3, 123.7, 127.0, 130.3, 130.8, 131.4, 136.4, 141.6, 150.1, 159.4; IR (KBr) 3178, 3127, 3043, 2857, 1677 (CO), 1588, 1549, 1460, 1270, 1221, 1158, 867, 809, 160, 751, 671, 629 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.22; H, 3.85; N, 14.30. Lit.[3a]

4.5.2. 6*H*-Benzo[*h*][1,6]naphthyridin-5-one 5b. Starting from **4b** and following the general procedure, the product was obtained as a white powder (0.48 g, 99%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H), 7.58 (td, J=1.5 and 7.3 Hz, 1H), 7.66 (dd, ^3J=4.6 Hz, ^3J=8.1 Hz, 1H), 8.56–8.62 (m, 2H), 9.05 (dd, ^4J=1.7 Hz, ^3J=4.6 Hz, 1H), 11.87 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.9, 118.8, 121.2, 122.4, 123.3, 124.0, 131.2, 135.7, 137.9, 150.5, 154.1, 160.8; IR (KBr) 3033, 2983, 2873, 1678 (CO), 1604, 1585, 1455, 1406, 1361, 1204, 1151, 884, 762, 731, 711, 668, 617, 496 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.19; H, 4.11; N, 14.08. Lit.[3a]

4.5.3. 6*H*-Benzo[*c*][2,7]naphthyridin-5-one 5c. Starting from **4c** and following the general procedure, the product was obtained as a white powder (0.46 g, 95%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.1 Hz, 1H), 7.38 (d, J=8.2 Hz, 1H), 7.68 (t, J=7.1 Hz, 1H), 8.41 (d, J=5.7 Hz, 1H), 8.45 (d, J=8.2 Hz, 1H), 8.90 (d, J=5.7 Hz, 1H), 9.41 (s, 1H), 11.94 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.7, 116.1, 116.4, 120.3, 122.6, 124.0, 131.2, 138.2, 140.6, 150.2, 151.8, 160.2; IR (KBr) 3016, 2887, 1682 (CO), 1603, 1476, 1417, 1357, 1180, 1041, 1018, 752, 730, 667 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.36; H, 4.08; N, 14.36. Lit.[3a,5]

4.5.4. 6*H*-Benzo[*c*][2,6]naphthyridin-5-one 5d. Starting from **4d** and following the general procedure, the product was obtained as a white powder (0.475 g, 98%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.54 (t, J=7.3 Hz, 1H), 8.10 (d, ^3J=5.1 Hz, 1H), 8.56 (d, J=8.0 Hz, 1H), 8.80 (d, ^3J=5.1 Hz, 1H), 9.88 (s, 1H), 12.07 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.7, 116.4, 119.6, 122.8, 123.0, 128.5, 130.4, 130.8, 136.9, 146.5, 147.8, 159.7; IR (KBr) 3024, 2997, 2874, 1669 (CO), 1609, 1549, 1469, 1432, 1411, 1368, 878, 748, 687, 639, 620, 508 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.13; H, 4.08; N, 13.96.

4.5.5. 5*H*-Phenanthridin-6-one 8. Starting from **7** and following the general procedure, the product was obtained as a white powder (0.39 g, 80%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.5 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.69 (t, J=7.5 Hz, 1H), 7.90 (t, J=7.5 Hz, 1H), 8.37 (d, J=8.0 Hz, 1H), 8.42 (d, J=8.0 Hz, 1H), 8.54 (d, J=8.0 Hz, 1H) 11.73 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=116.1, 117.5, 122.2, 122.6, 123.2, 125.6, 127.4, 127.9, 129.5, 132.7, 134.2, 136.5, 160.8; IR (KBr) 3435, 3047, 1663 (CO), 1608, 1557, 1510, 1469, 1424, 1369, 1153, 1037, 943, 748, 726 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 79.98; H, 4.65; N, 7.17. Found: C, 79.84; H, 4.52; N, 6.72. Lit.[15]

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References and notes

1. (a) Roseman, K. A.; Gould, M. M.; Linfiel, W. M.; Edwards, B. E. *J. Med. Chem.* **1970**, *13*, 230; (b) Loy, M.; Joullie, M. M. *J. Med. Chem.* **1973**, *16*, 549; (c) Yapi, A. D.; Mustofa, M.; Valentin, A.; Chavignon, O.; Teulade, J. C.; Mallie, M.; Chapat, J. P.; Blache, Y. *Chem. Pharm. Bull.* **2000**,

48, 1886; (d) Hinschberger, A.; Butt, S.; Lelong, V.; Boulouard, M.; Dumuis, A.; Dauphin, F.; Bureau, R.; Pfeiffer, B.; Renard, P.; Rault, S. *J. Med. Chem.* **2003**, *46*, 138.

2. For examples of biological activities in 6-substituted phenanthridines series see: (a) Kock, I.; Heber, D.; Weide, M.; Wolschendorf, U.; Clement, B. *J. Med. Chem.* **2005**, *48*, 2772; (b) Parenty, A. D. C.; Smith, L. V.; Guthrie, K. M.; Long, D.; Plumb, J.; Brown, R.; Cronin, L. *J. Med. Chem.* **2005**, *48*, 4504; For examples of biological activities in 6-substituted benzo[*c*]phenanthridine series see: (c) Vogt, A.; Tamewitz, A.; Skoko, J.; Sikorski, J. S.; Giuliano, K. A.; Lazo, J. S. *J. Biol. Chem.* **2005**, *280*, 19078; (d) Prado, S.; Michel, S.; Tillequin, F.; Koch, M.; Pfeiffer, B.; Pierré, A.; Léonce, S.; Colson, P.; Baldeyrou, B.; Lansiaux, A.; Bailly, C. *Bioorg. Med. Chem.* **2004**, *12*, 3943; (e) Nyangulu, J. M.; Hargreaves, S. L.; Sharples, S. L.; Mackay, S. P.; Waigh, R. D.; Duval, O.; Mberu, E. K.; Watkins, W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2007.
3. (a) Ferraris, D.; Ko, Y. S.; Pahutski, T.; Ficco, R. P.; Serdyiuk, L.; Alemu, C.; Bradford, C.; Chiou, T.; Hoover, R.; Huang, S.; Lautar, S.; Liang, S.; Lin, Q.; Lu, M. X. C.; Mooney, M.; Morgan, L.; Qian, Y.; Tran, S.; Williams, L. R.; Wu, Q. Y.; Zhang, J.; Zou, Y.; Kalish, V. *J. Med. Chem.* **2003**, *46*, 3138; (b) Hamada, Y.; Isao, T. *Chem. Pharm. Bull.* **1976**, *24*, 2679.
4. (a) Vinick, F. J.; Desai, M. C.; Jung, S.; Thadeio, P. *Tetrahedron Lett.* **1989**, *30*, 787; (b) Kobayashi, Y.; Kumadaki, I.; Morinaga, K. *Chem. Pharm. Bull.* **1969**, *17*, 1511.
5. Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292.
6. (a) Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *2*, 257; (b) Pawlas, J.; Begtrup, M. *Org. Lett.* **2002**, *16*, 2687; (c) Kristensen, J. L.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2003**, *68*, 4091.
7. Hansen, H. M.; Lysén, M.; Begtrup, M.; Kristensen, J. L. *Tetrahedron* **2005**, *61*, 9955.
8. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Org. Chem.* **1999**, *576*, 147; (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1991**, 207.
9. (a) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323; (b) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.
10. Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Sopkova, J.; Rault, S. *Synlett* **2006**, 53.
11. Urawa, Y.; Naka, H.; Miyazawa, M.; Souda, S.; Ogura, K. *J. Organomet. Chem.* **2002**, *653*, 269.
12. Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett.* **2005**, *46*, 135.
13. (a) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *11*, 2101; (b) Hayashi, K.; Kim, S.; Kono, Y.; Tamura, M.; Chiba, K. *Tetrahedron Lett.* **2006**, *47*, 171; (c) Miao, G.; Ye, P.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *76*, 2332.
14. Rokach, J.; Girard, Y. *J. Heterocycl. Chem.* **1978**, *15*, 683.
15. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.