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Tetrahedron
Tetrahedron 63 (2007) 71–76

The synthesis of three new heterocycles: the pyrido[4,3 or 3,4 or 2,3-*c*]-1,5-naphthyridines

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Received 19 September 2006; revised 18 October 2006; accepted 19 October 2006
Available online 13 November 2006

Abstract—Pyrido[4,3 or 3,4 or 2,3-*c*]-1,5-naphthyridines were obtained with good yields after chlorodehydroxylation and dehalogenation reactions starting from the parent pyridonaphthyridinones. These pyridonaphthyridinones were synthesized in a two-step procedure using a Suzuki cross-coupling reaction between 2-chloro-3-fluoropyridine and orthocyanopyridylboronic esters followed by a KOH-mediated anionic ring closure.

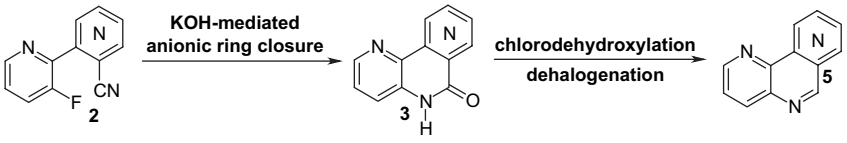
1. Introduction

The pyridonaphthyridines, which result from the fusion of three pyridines without bridged nitrogen are of a difficult chemical access and among all the 16 possible isomers only a few publications describe the synthesis of five isomers. Case[1] and Hamada[2] described the synthesis of the pyrido[3,2-*c*]-1,5-naphthyridine by the use of a Skraup reaction starting from aminonaphthyridines. Czuba[3] also used this strategy for the synthesis of the pyrido[2,3-*c*]-1,5-naphthyridine. But none of these papers described a clear protocol. Nutaitis[4] used a multistep synthesis starting from 2- or 3-aminopyridine and 5-bromopyridine-3-carboxaldehyde to obtain, with respectively 11 and 13% overall yield, the pyrido[3,4-*c*]-1,7-naphthyridine and the pyrido[3,4-*c*]-1,8-naphthyridine. Williams[5] used a thermal reaction of bisacylazido-3,3′-bipyridine to obtain the pyrido[3,2-*c*]-1,8-naphthyridine via a double Curtius rearrangement. None of these methods appear to be useable to produce pyridonaphthyridines as valuable scaffolds in medicinal chemistry.

In this article we took into account our experience in the synthesis of pyridylboronic acids[6] and their use in the Suzuki cross-coupling reaction to give oligopyridines,[7] and moreover, our results demonstrated that ortho-2-fluorophenylcyanopyridines could undergo intramolecular KOH anionic ring closure to give benzonaphthyridinones.[8] The enlargement of these methodologies (Scheme 1) for the obtention of bipyridinic systems **2** and their use in an intramolecular reaction, allows us to describe for the first time an original route to obtain pyridonaphthyridinones **3**, which permit after a chlorodehydroxylation and a dehalogenation process, an efficient synthesis of pyridonaphthyridines **5** such as pyrido[4,3-*c*]-1,5-naphthyridine **5a**, pyrido[3,4-*c*]-1,5-naphthyridine **5b** and pyrido[2,3-*c*]-1,5-naphthyridine **5c**.

2. Results and discussion

The required bipyridines **2** were synthesized by a Suzuki cross-coupling reaction from the commercially available



Scheme 1. Our strategy for the synthesis of some pyridonaphthyridines.

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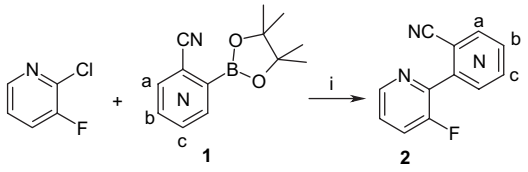
doi:10.1016/j.tet.2006.10.046

2-chloro-3-fluoropyridine and an orthocyanopyridylboronic pinacol ester **1**, we had recently described the synthesis.[9] Unfortunately, these esters revealed an unstable profile in the standard Suzuki cross-coupling conditions since they were proned to protodeboronation. Begtrup's group showed that the use of the CuI/CsF couple as co-catalyst and base in dioxane at 60 °C for 5 h with pyridylboronic neopentylglycol esters favoured the cross-coupling instead of the protodeboronation reaction (60–80% yield).[10] However, when we applied these conditions to our pinacol esters, we only recovered after 5 h the unchanged starting materials. Recent results from our laboratory and others in microwave assisted Suzuki cross-coupling[11] reactions prompted us to use this now commonly accepted routine methodology. As dioxane is a poor microwave solvent because of its low polarity, we used DMF to perform the reaction. The total conversion of 2-chloro-3-fluoropyridine was observed after heating for 30 min at 150 °C under microwave irradiation, provided that 2 equiv of orthocyanopyridylboronic pinacol esters **1a–c** was used (Table 1).

The bipyridines **2** were then submitted to a KOH-mediated anionic ring closure, which was realized under microwave heating conditions. For **2a** and **2c**, the reaction required a 10 min reaction time, whereas 30 min was needed for **2b** (Table 2). The three expected pyrido[*c*]-1,5-naphthyridin-6-ones **3** were isolated in 78–81% yield.[12] They were then submitted to a chlorodehydroxylation reaction using phosphorus oxychloride at 100 °C for 12 h. The 6-chloropyrido[*c*]-1,5-naphthyridines **4** were easily obtained in good yields.

In order to access to the parent pyrido[*c*]-1,5-naphthyridines, the 6-chloropyrido[*c*]-1,5-naphthyridines **4** were submitted to a dehalogenation reaction. Among the numerous dehalogenation methods, we decided to use a catalytic transfer hydrogenation reaction recently described by Schlosser et al.[13] on chloropyridines using ammonium formate and palladium on charcoal in alcoholic solvent. First, we tried this methodology with the 6-chloropyrido[4,3-*c*]-1,5-naphthyridine **4c**. After 12 h of stirring in MeOH with 4 equiv of ammonium formate, the LC/MS monitoring of the reaction showed a total conversion of **4c** and the formation of two products: the expected pyrido[4,3-*c*]-1,5-naphthyridine **5c** and a hydrogenated product, which could be 5,6-dihydropyrido[4,3-*c*]-1,5-naphthyridine **6** (MW=183 g mol^{-1} given by LC/MS). Our attempts to separate this two products remained inefficient. Compound **6** seemed to slowly oxidize into pyrido[4,3-*c*]-1,5-naphthyridine **5c** on silica gel or under an air oxygen. This result prompted us to add DDQ[14] to the crude mixture. The LC/MS showed a total conversion into pyrido[4,3-*c*]-1,5-naphthyridine **5c**, which was isolated in a 87% yield (Scheme 2).

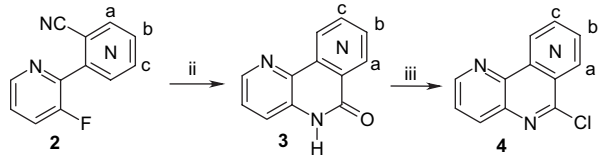
Table 1. Microwave Suzuki cross-coupling of 2-chloro-3-fluoropyridine and orthocyanopyridylboronic pinacol ester



Starting materials	Products	Yields (%)
1a	**2a**	60[a]
1b	**2b**	72[a]
1c	**2c**	88[a]

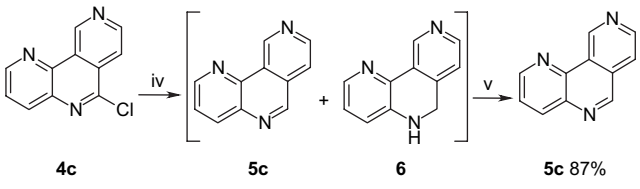
[a] Isolated yields. Reagents and conditions: (i) 1 equiv of aromatic halide, 2 equiv of boronic ester, 5 mol % of $Pd(PPh_3)_4$, 10 mol % of CuI, 2.5 equiv of CsF, DMF, 150 °C, sealed tube, microwave heating, 30 min.

Table 2. KOH anionic ring closure followed by chlorodehydroxylation



KOH anionic ring closure			Chlorodehydroxylation	
Starting materials	Products	Yields (%)	Products	Yields (%)
2a	**3a**	81[a]	**4a**	76[a]
2b	**3b**	78[a,b]	**4b**	73[a]
2c	**3c**	80[a]	**4c**	72[a]

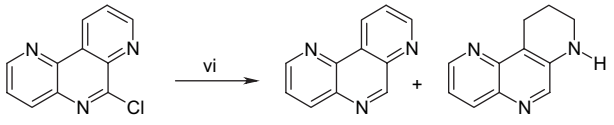
[a] Isolated yields.
[b] Reaction time increased to 30 min. Reagents and conditions: (ii) KOH 5 equiv, MeOH, 150 °C, sealed tube, microwave heating, 10 min and (iii) $POCl_3$, 100 °C, 12 h.



Scheme 2. Dehalogenation of 6-chloropyrido[4,3-*c*]-1,5-naphthyridine **4c** into pyrido[4,3-*c*]-1,5-naphthyridine **5c** (isolated yield). Reagents and conditions: (iv) HCO_2NH_4 4 equiv, 10 mol % of Pd/C, MeOH, rt, 12 h and (v) DDQ 1 equiv, DCM, rt, 1 h.

Starting from 6-chloropyrido[2,3-*c*]-1,5-naphthyridine **4a** and using the same conditions as for **4c** (Table 3, entry 1) only unchanged starting material was recovered. By heating the reaction mixture to reflux, the dehalogenation occurred and the LC/MS this time showed after 3 h a total conversion of the 6-chloropyrido[2,3-*c*]-1,5-naphthyridine **4a** and the

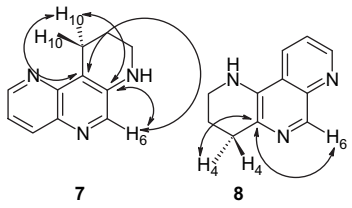
Table 3. Dehalogenation of 6-chloropyrido[2,3-*c*]-1,5-naphthyridine **4a** into pyrido[2,3-*c*]-1,5-naphthyridine **5a**



Entry	Temperature	HCO_2NH_4 (equiv)	Time (h)	**5a** Yields (%)	**7** Yields (%)
1	rt	4	12	0	0
2	Reflux	4	3	24[a]	46[a]
3	Reflux	1	24	81[a]	0

[a] Isolated yields. Reagents and conditions: (vi) HCO_2NH_4, 10 mol % of Pd/C, MeOH.

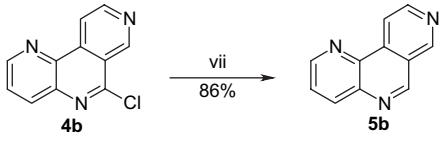
formation of two products, the expected pyrido[2,3-*c*]-1,5-naphthyridine **5a**, and a product of molecular weight 185 g mol^{-1}. After purification, classical NMR experiments revealed that our unknown product was 7,8,9,10-tetrahydropyrido[2,3-*c*]-1,5-naphthyridine **7** or 1,2,3,4-tetrahydropyrido[2,3-*c*]-1,5-naphthyridine **8**. HMBC NMR experiment showed two common proton–carbon (^2J–^3J) correlations between two quaternary carbons and protons H_6 and H_{10} or H_4. Only one quaternary carbon can present this correlation for compound **8** (Scheme 3). Our unknown structure was 7,8,9,10-tetrahydropyrido[2,3-*c*]-1,5-naphthyridine **7** (Table 3, entry 2).



Scheme 3. Comparison of possible common proton–carbon (^2J–^3J) correlations for H_6 and H_9 or H_4.

In order to avoid the formation of 7,8,9,10-tetrahydropyrido[2,3-*c*]-1,5-naphthyridine **7**, we postulated that the formation of this compound was more difficult regarding to the dehalogenation reaction. So, we decided to exploit this difference by reacting 6-chloropyrido[2,3-*c*]-1,5-naphthyridine **4a** with 1 equiv of ammonium formate (Table 3, entry 3). The LC/MS monitoring showed after 24 h the total conversion of **4a** into **5a** and the absence of **7**. Pyrido[2,3-*c*]-1,5-naphthyridine **5a** was isolated with a 81% yield.

Finally, 6-chloropyrido[3,4-*c*]-1,5-naphthyridine **4b** was submitted to these latter conditions. The reaction this time was achieved in 3 h and afforded the pyrido[3,4-*c*]-1,5-naphthyridine **5b** in a high 86% yield (Scheme 4). The use of these conditions with the 6-chloropyrido[4,3-*c*]-1,5-naphthyridine **4c** did not permit to obtain the expected pyrido[4,3-*c*]-1,5-naphthyridine **5c** without the formation of the hydrogenated compound **6**. The best conditions for **4c** remains the use of 4 equiv of ammonium formate (Scheme 2) allowing the total conversion of the starting material and to isolate the pyrido[4,3-*c*]-1,5-naphthyridine **5c** with a good yield.



Scheme 4. Dehalogenation of 6-chloropyrido[3,4-*c*]-1,5-naphthyridine **4b** into pyrido[3,4-*c*]-1,5-naphthyridine **5b** (isolated yield). Reagents and conditions: (vii) HCO_2NH_4 1 equiv, 10 mol % of Pd/C, MeOH, reflux, 3 h.

3. Conclusion

In conclusion, we have established that KOH-mediated ring closure allows the generation of new pyridine based heterotricyclic structures such as the parent pyridonaphthyridines. To our knowledge, all the synthesized intermediates are new. Moreover, the 6-chloropyrido[*c*]-1,5-naphthyridines **4a–c** could be interesting building blocks for the obtention of new 6-substituted pyrido[*c*]-1,5-naphthyridines with great potential interest in medicinal chemistry. Our studies also revealed noticeable differences in the reactivity among the three structures. In the future, our methodology should be applied to the synthesis of new isomers of pyridonaphthyridines and we plan to extend this method to other heterocyclic systems.

4. Experimental section

4.1. General

Melting points were determined on a Kofler melting point apparatus. IR spectrum was recorded with a Perkin Elmer BX FT-IR. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz with a Jeol Lambda 400 NMR spectrometer except for **5a**, **5b** and **5c** for which the spectrometers are mentioned in the Section 4.8. The microwave reactions were performed using a Biotage Initiator microwave oven. Temperature was measured with an IR-sensor and reaction is given as hold times.

4.2. General procedure for Suzuki cross-coupling

In a microwave vial was introduced a magnetic stir bar, CsF (2.0 g, 12.9 mmol), the chosen orthocyanopyridylboronic ester (2.4 g, 10.5 mmol), CuI (0.1 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.3 g, 0.25 mmol). The vial was sealed and purged with argon through the septum inlet. A solution of 2-chloro-3-fluoropyridine (0.68 g, 5.2 mmol) was degassed with argon and added with a syringe through the vial's septum. The suspension was then heated at 150 °C for 30 min. The resulting mixture was poured into 75 mL of water and extracted three times with 100 mL of EtOAc. The combined organic layers were washed three times with 50 mL of brine, dried with $MgSO_4$, filtered and evaporated. The crude product was then purified by silica gel chromatography.

4.2.1. 3-Fluoro-2,3′-bipyridine-2′-carbonitrile 2a. Starting from 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine-2-carbonitrile **1a**, following the general procedure and using DCM and DCM/EtOAc (8/2) as eluents for the column chromatography, the product was obtained as a yellow powder (0.90 g, 88%). Mp 91 °C; IR (KBr) 3079, 2925, 2239 (CN), 1637, 1594, 1581, 1466, 1450, 1431, 1413, 1407, 1263, 1250, 1195, 1174, 1096, 1069, 1019, 812, 771, 685, 581, 555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.46–7.50 (m, 1H), 7.61–7.66 (m, 2H), 8.09 (dt, J=8.1 Hz, 1.3 Hz, 1H), 8.63 (dt, J=4.6 Hz, 1.4 Hz, 1H), 8.75 (dd, ^3J=8.8 Hz, ^4J=1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.3, 124.5 (d, J=19 Hz), 126.1 (d, J=4 Hz), 126.3, 133.3 (d, J=2 Hz), 135.7 (d, J=5 Hz), 138.8 (d, J=3 Hz), 141.7 (d, J=12 Hz), 146.1 (d, J=5 Hz), 150.7, 157.4 (d, ^1J=260 Hz); HRMS/EI (g mol^{-1}) calcd for $C_{11}H_6FN_3$ 199.0546, found 199.0554.

4.2.2. 3-Fluoro-2,4′-bipyridine-3′-carbonitrile 2b. Starting from 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinonitrile **1b**, following the general procedure and using DCM and DCM/EtOAc (9/1) as eluents for the column chromatography, the product was obtained as a yellow

powder (0.52 g, 72%). Mp 102 °C; IR (KBr) 3072, 2225 (CN), 1584, 1544, 1432, 1403, 1249, 1183, 1099, 1064, 842, 801, 733, 702, 624, 587, 552, 508, 557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.48–7.53 (m, 1H), 7.61–7.66 (m, 1H), 7.72 (d, ^3J=5.1 Hz, 1H), 8.64 (dt, J=4.6 Hz, 1.5 Hz, 1H), 8.91 (d, ^3J=5.1 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=109.4, 115.9, 124.2 (d, J=5 Hz), 124.8 (d, J=19 Hz), 126.6 (d, J=4 Hz), 141.3 (d, J=12 Hz), 145.5 (d, J=5 Hz), 146.6 (d, J=5 Hz), 152.7, 153.9, 157.3 (d, ^1J=261 Hz); HRMS/EI (g mol^{-1}) calcd for $C_{11}H_6FN_3$ 199.0546, found 199.0532.

4.2.3. 3-Fluoro-2,3′-bipyridine-4′-carbonitrile 2c. Starting from 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isonicotinonitrile **1c**, following the general procedure and using DCM and DCM/EtOAc (9/1) as eluents for the column chromatography, the product was obtained as a yellow powder (0.62 g, 60%). Mp 92 °C; IR (KBr) 3073, 2233 (CN), 1593, 1583, 1493, 1434, 1407, 1253, 1217, 1184, 1077, 845, 816, 803, 773, 740, 637, 590, 557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.47–7.51 (m, 1H), 7.62–7.67 (m, 1H), 7.71 (d, ^3J=4.6 Hz, 1H), 8.65 (dt, J=4.6 Hz, 1.4 Hz, 1H), 8.86 (br s, 1H), 9.09 (br s, 1H); ^1H NMR (400 MHz, DMSO) δ=7.66–7.71 (m, 1H), 7.98–8.03 (m, 1H), 8.06 (d, ^3J=5.1 Hz, 1H), 8.65 (dt, J=4.4 Hz, 1.4 Hz, 1H), 8.93 (d, ^3J=5.1 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.7, 119.2, 124.9 (d, J=20 Hz), 126.8, 126.83, 126.88, 131.6 (d, J=5 Hz), 140.5 (d, J=13 Hz), 146.3 (d, J=5 Hz), 150.9 (d, J=4 Hz), 156.9 (d, ^1J=258 Hz); HRMS/EI (g mol^{-1}) calcd for $C_{11}H_6FN_3$ 199.0546, found 199.0543.

4.3. General procedure for KOH anionic ring closure

The chosen bipyridine **2** (0.5 g, 2.5 mmol) and KOH (0.7 g, 12.5 mmol) were solubilized in MeOH (5 mL) in microwave vial. The suspension was then heated at 150 °C 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. The crude product was then washed with acetonitrile and filtered to give analytically pure product **3**.

4.3.1. Pyrido[2,3-*c*]-1,5-naphthyridin-6(5*H*)-one 3a. Starting from **2a** and following the general procedure the product was obtained as a white powder. Mp >260 °C; IR (KBr) 3043, 2978, 2841, 1717 (CO), 1667, 1589, 1559, 1451, 1413, 1350, 1299, 1259, 1202, 1147, 1100, 1064, 1020, 869, 803, 757, 713, 675, 639, 619, 583 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ=7.56 (dd, ^3J=8.2 Hz, ^3J=4.4 Hz, 1H), 7.74 (dd, ^3J=8.2 Hz, ^4J=1.2 Hz, 1H), 7.89 (dd, ^3J=8.1 Hz, ^3J=4.4 Hz, 1H), 8.55 (dd, ^3J=4.4 Hz, ^4J=1.2 Hz, 1H), 8.99 (dd, ^3J=4.4 Hz, ^4J=1.5 Hz, 1H), 9.09 (dd, ^3J=8.1 Hz, ^4J=1.5 Hz, 1H), 11.87 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=124.2, 125.8, 128.1, 132.6, 133.8, 135.1, 143.9, 145.0, 152.3, 160.0 (a quaternary carbon's signal wasn't observed); HRMS/EI (g mol^{-1}) calcd for $C_{11}H_7N_3O$ 197.0589, found 197.0587.

4.3.2. Pyrido[3,4-*c*]-1,5-naphthyridin-6(5*H*)-one 3b. Starting from **2b** and following the general procedure but the reaction time has to be extended to 30 min the product was obtained as a white powder. Mp >260 °C; IR (KBr) 3014, 2953, 2885, 1687 (CO), 1678, 1604, 1593, 1502, 1480, 1462, 1415, 1355, 1280, 1121, 1031, 910, 845, 810, 672, 643 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ=7.64 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 7.75 (dd, ^3J=8.3 Hz, ^4J=0.9 Hz, 1H), 8.52 (d, ^3J=5.3 Hz, 1H), 8.60 (dd, ^3J=4.4 Hz, ^4J=0.9 Hz, 1H), 8.98 (d, ^3J=5.3 Hz, 1H), 9.44 (s, 1H), 11.99 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.8, 121.5, 123.7, 126.0, 133.1, 134.5, 140.9, 144.3, 149.7, 151.9, 159.6; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_7N_3O$ 197.0589, found 197.0592.

4.3.3. Pyrido[4,3-*c*]-1,5-naphthyridin-6(5*H*)-one 3c. Starting from **2c** and following the general procedure the product was obtained as a white powder (0.4 g, 80%). Mp >260 °C; IR (KBr) 3018, 2924, 2860, 1669 (CO), 1553, 1474, 1359, 1303, 1275, 1186, 1110, 1014, 910, 848, 808, 754, 693, 681, 638, 578 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ=7.55 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 7.74 (dd, ^3J=8.3 Hz, ^4J=1.4 Hz, 1H), 8.10 (d, ^3J=5.1 Hz, 1H), 8.57 (dd, ^3J=4.4 Hz, ^4J=1.4 Hz, 1H), 8.90 (d, ^3J=5.1 Hz, 1H), 9.97 (s, 1H), 12.08 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=119.4, 123.7, 125.0, 128.7, 132.4, 133.2, 133.8, 144.4, 146.5, 149.3, 159.3; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_7N_3O$ 197.0589, found 197.0585.

4.4. General procedure for chlorodehydroxylation

The chosen pyridonaphthyridinone **3** (0.40 g, 2 mmol) was heated at 100 °C in $POCl_3$ (10 mL), for 12 h (TLC monitoring). The resulting mixture was poured carefully drop by drop into cold water and the pH was adjusted to 10 using a 28% aqueous ammonia solution. The resulting solution was extracted three times with EtOAc, dried with $MgSO_4$, filtered and evaporated. The crude product was then purified by silica gel chromatography.

4.4.1. 6-Chloropyrido[3,4-*c*]-1,5-naphthyridine 4a. Starting from **3a**, following the general procedure and using DCM/EtOAc (1/1) as eluent for the column chromatography, the product was obtained as a white powder (0.32 g, 73%). Mp 194 °C; IR (KBr) 3054, 2924, 1607, 1558, 1561, 1500, 1446, 1422, 1399, 1337, 1321, 1282, 1259, 1177, 1107, 1031, 971, 957, 852, 801, 736, 621, 529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.80 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 8.42 (dd, ^3J=8.3 Hz, ^4J=1.7 Hz, 1H), 8.94 (d, ^3J=5.5 Hz, 1H), 9.03 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 9.12 (d, ^3J=5.5 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.3, 121.7, 126.2, 136.6, 139.37, 139.39, 140.1, 140.3, 150.43, 150.45, 150.7; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_6ClN_3$ 215.0250, found 215.0245.

4.4.2. 6-Chloropyrido[2,3-*c*]-1,5-naphthyridine 4b. Starting from **3b**, following the general procedure and using DCM/EtOAc (1/1) as eluent for the column chromatography, the product was obtained as a white powder (0.33 g, 76%). Mp 196 °C; IR (KBr) 3427, 3050, 1732, 1561, 1451, 1421, 1317, 1291, 1252, 1173, 987, 791, 755, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=7.76 (dd, ^3J=8.4 Hz, ^3J=4.4 Hz, 1H), 7.93 (dd, ^3J=8.2 Hz, ^3J=4.4 Hz, 1H), 7.74 (dd, ^3J=8.4 Hz, ^4J=1.7 Hz, 1H), 9.04 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 9.26 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 9.51 (dd, ^3J=8.2 Hz, ^4J=1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=124.8, 126.4, 130.8, 132.4, 136.3, 138.2, 139.9, 140.6, 150.1, 152.4,

153.2; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_6ClN_3$ 215.0250, found 215.0253.

4.4.3. 6-Chloropyrido[4,3-*c*]-1,5-naphthyridine 4c. Starting from **3c**, following the general procedure and using DCM/EtOAc (2/1) as eluent for the column chromatography, the product was obtained as a white powder (0.31 g, 72%). Mp 191 °C; IR (KBr) 3049, 1603, 1570, 1457, 1393, 1316, 1281, 1209, 1167, 106, 982, 802, 767, 746, 724, 639, 605, 575 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.76 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 8.20 (dd, ^3J=5.7 Hz, ^4J=0.6 Hz, 1H), 8.42 (dd, ^3J=8.3 Hz, ^4J=1.7 Hz, 1H), 9.08–9.10 (m, 2H), 10.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=118.8, 125.1, 128.4, 130.6, 136.5, 139.2, 139.7, 148.9, 148.9, 150.7, 150.9; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_6ClN_3$ 215.0250, found 215.0259.

4.5. Synthesis of pyrido[4,3-*c*]-1,5-naphthyridine 5c

6-Chloropyrido[4,3-*c*]-1,5-naphthyridine **4c** (0.100 g, 0.45 mmol), ammonium formate (0.117 g, 1.85 mmol) and Pd/C 10% (0.049 g, 0.045 mmol) were stirred for 12 h (LC/MS monitoring) in methanol (20 mL). The solution was filtered through paper, evaporated and solubilized with DCM (20 mL) before addition of DDQ (0.105 g, 0.45 mmol). The mixture was allowed to stir for 1 h, diluted with DCM (30 mL), washed three times with 40 mL of a saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered and evaporated. The crude product was then purified by silica gel chromatography using DCM/EtOAc (1/1)+3% MeOH as eluent to give pyrido[4,3-*c*]-1,5-naphthyridine **5c** as white powder (0.073g, 87%). Mp 142 °C; IR (KBr) 3050, 2963, 2927, 1729, 1586, 1562, 1484, 1452, 1415, 1380, 1280, 1241, 1154, 1096, 1038, 1013, 954, 790, 739, 724, 632, 620, 502, 457 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=7.80 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 7.94 (d, ^3J=5.4 Hz, 1H), 8.53 (dd, ^3J=8.3 Hz, ^4J=1.7 Hz, 1H), 9.07 (d, ^3J=5.4 Hz, 1H), 9.07 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 9.44 (s, 1H), 10.55 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ=118.7, 124.0, 126.2, 130.2, 136.9, 139.2, 139.4, 147.3, 147.9, 150.2, 152.3; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_7N_3$ 181.0640, found 181.0649.

4.6. Synthesis of pyrido[2,3-*c*]-1,5-naphthyridine 5a and 7,8,9,10-tetrahydropyrido[2,3-*c*]-1,5-naphthyridine 7

4.6.1. Using 4 equiv of ammonium formate. 6-Chloropyrido[2,3-*c*]-1,5-naphthyridine **4a** (0.100 g, 0.45 mmol), ammonium formate (0.117 g, 1.85 mmol) and Pd/C 10% (0.049 g, 0.045 mmol) were stirred for 3 h (LC/MS monitoring) in refluxing methanol (20 mL). The solution was filtered through paper and evaporated. The crude product was then purified by silica gel chromatography using DCM/EtOAc (1/1)+3% MeOH as eluent to give pyrido[2,3-*c*]-1,5-naphthyridine **5a** as white powder (0.020 g, 24%) and 7,8,9,10-tetrahydropyrido[2,3-*c*]-1,5-naphthyridine **7** (0.040 g, 46%) as a yellow oil.

4.6.2. Using 1 equiv of ammonium formate. 6-Chloropyrido[2,3-*c*]-1,5-naphthyridine **4a** (0.100 g, 0.45 mmol), ammonium formate (0.030 g, 0.45 mmol) and Pd/C 10% (0.049 g, 0.045 mmol) were stirred for 24 h (LC/MS monitoring) in refluxing methanol (20 mL). The solution was filtered through paper and evaporated. The crude product was then purified by silica gel chromatography using DCM/EtOAc (1/1)+3% MeOH eluent to give pyrido[2,3-*c*]-1,5-naphthyridine **5a** as white powder (0.68 g, 81%).

4.6.3. Pyrido[2,3-*c*]-1,5-naphthyridine 5a. Mp 123 °C; IR (KBr) 3260, 2924, 2854, 1591, 1570, 1455, 1378, 1324, 1219, 1129, 1187, 1129, 1096, 1056, 937, 836, 778, 739, 614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.77 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 7.87 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 8.54 (dd, ^3J=8.3 Hz, ^4J=1.7 Hz, 1H), 9.05 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 9.17 (dd, ^3J=4.4 Hz, ^4J=1.7 Hz, 1H), 9.46 (ddd, ^3J=8.3 Hz, ^4J=1.7 Hz, ^4J=0.8 Hz, 1H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=124.8, 126.3, 129.7, 132.2, 137.9, 139.7, 140.6, 144.1, 150.5, 152.9, 156.1; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_7N_3$ 181.0640, found 181.0644.

4.6.4. 7,8,9,10-Tetrahydropyrido[2,3-*c*]-1,5-naphthyridine 7. IR (KBr) 3306 (NH), 2940, 2857, 1713, 1671, 1588, 1576, 1523, 1483, 1343, 1298, 1219, 1100, 914, 815, 801, 776, 757, 675, 638, 618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.08 (m, 2H), 3.25 (t, ^3J=6.3 Hz, 2H), 3.44 (t, J=4.3 Hz, 2H), 4.31 (br s, 1H), 7.32 (dd, ^3J=8.3 Hz, ^3J=4.4 Hz, 1H), 8.17 (dd, ^3J=8.3 Hz, ^4J=1.5 Hz, 1H), 8.34 (s, 1H), 8.81 (dd, ^3J=4.4 Hz, ^4J=1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.0, 21.2, 41.5, 119.9, 121.2, 136.9, 137.4, 141.4, 143.5, 144.0, 150.4; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_{11}N_3$ 185.0953, found 185.0948.

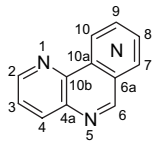
4.7. Synthesis of pyrido[3,4-*c*]-1,5-naphthyridine 5b

6-Chloropyrido[3,4-*c*]-1,5-naphthyridine **4b** (0.100 g, 0.45 mmol), ammonium formate (0.030 g, 0.45 mmol) and Pd/C 10% (0.049 g, 0.045 mmol) were stirred for 3 h (LC/MS monitoring) in refluxing methanol (20 mL). The solution was filtered through paper and evaporated. The crude product was then purified by silica gel chromatography using DCM/EtOAc (1/1)+3% MeOH as eluent to give pyrido[3,4-*c*]-1,5-naphthyridine **5b** as white powder (0.72 g, 86%). Mp 146 °C; IR (KBr) 2924, 1727, 1610, 1578, 1506, 1447, 1384, 1281, 1261, 1224, 1110, 1020, 898, 848, 799, 735, 620, 559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.83 (dd, ^3J=8.3 Hz, ^3J=4.3 Hz, 1H), 8.54 (dd, ^3J=8.3 Hz, ^4J=1.5 Hz, 1H), 8.94 (d, ^3J=5.6 Hz, 1H), 9.08 (d, ^3J=5.6 Hz, 1H), 9.10 (dd, ^3J=4.3 Hz, ^4J=1.5 Hz, 1H), 9.50 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.7, 123.5, 126.1, 138.0, 138.5, 139.9, 141.5, 150.1, 150.7, 152.0, 153.4; HRMS/EI (g mol^{-1}) calcd for $C_{11}H_7N_3$ 181.0640, found 185.0635.

4.8. Pyridonaphthyridines 5a,b,c ^{1}H and ^{13}C NMR assignments

For **5c**, NMR experiments were achieved at 300 K on a Bruker DMX 600 spectrometer equipped with a 5 mm triple resonance {^{1}H (600.13 MHz), ^{13}C (150.90 MHz), ^{15}N (60.81 MHz)} Cryoprobe including shielded z-gradients. Internal reference from $CDCl_3$ (δ_H=7.26, δ_C=77.36). For **5a** and **5b**, NMR experiments were achieved at 296 K on a Bruker DRX 400 spectrometer equipped with a 5 mm quadripolar nuclear probe {^{1}H (400.13 MHz), ^{13}C (100.62 MHz), ^{19}F (376.50 MHz), ^{31}P (161.98 MHz)} including shielded z-gradients. Internal reference from $CDCl_3$ (δ_H=7.26 and δ_C=77.36) (Table 4).

Table 4. Pyridonaphthyridines **5a**,**b**,**c** ^{1}H and ^{13}C NMR chemical shifts assignement by HMBC and HMQC[a]



No.	**5c**	**5b**	**5a**
1	N	N	N
2	150.2, *9.07*	150.7, *9.10*	150.5, *9.05*
3	124.0, *7.80*	126,1, *7.83*	124,8, *7.77*
4	136.9, *8.53*	138.0, *8.54*	137.9, *8.54*
4a	139.4	141.5	139.7
5	N	N	N
6	152.3, *9.44*	153.4, *9.50*	156.1, *9.62*
6a	130.2	123.5	144.1
7	118.7, *7.94*	152.0, *9.52*	N
8	147.3, 9.07	N	152.9, 9.17
9	N	150.1, *9.08*	126.3, *7.87*
10	147.9, *10.55*	116.7, *8.94*	132.2, *9.46*
10a	126.2	138.5	129.7
10b	139.2	139.9	140.6

[a] ^{1}H chemical shifts are in italic, ^{13}C in regular and both are expressed in parts per million.

Acknowledgements

We thank 'Les Laboratoires Servier', The 'Conseil Régional de Basse-Normandie' and 'Les Sapins de l'Espoir' for their financial support.

References and notes

1. Case, F. H.; Brennan, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 6297–6301.
2. Hamada, Y.; Sato, M.; Takeuchi, I. *Yakugaku Zasshi* **1975**, *95*, 1492–1497.
3. Czuba, W. *Rocz. Chem.* **1967**, *41*, 289–297.
4. Nutaitis, C. F.; Brennan, M. *Org. Prep. Proced. Int.* **2004**, *36*, 367–370.
5. Williams, R. L.; ElFayoumy, M. G. *J. Heterocycl. Chem.* **1972**, *9*, 1021–1025.
6. (a) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885–2890; (b) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323–3328; (c) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369–4373.
7. Bouillon, A.; Voisin, A. S.; Robic, A.; Lancelot, J. C.; Collot, V.; Rault, S. *J. Org. Chem.* **2003**, *68*, 10178–10180.
8. Cailly, T.; Fabis, F.; Rault, S. *Tetrahedron* **2006**, *62*, 5862–5867.
9. Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Sopkova, J.; Rault, S. *Synlett* **2006**, 53–56.
10. Hansen, H. M.; Lysén, M.; Begtrup, M.; Kristensen, J. *Tetrahedron* **2005**, *61*, 9955–9960.
11. For a general review, see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; Suzuki cross-coupling: (a) Miao, G.; Ye, P.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *76*, 2332–2334; (b) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *11*, 2101–2104.
12. Two references describe the synthesis of compound **3a**. (a) Mannich, C.; Abdullah, S. M. *Ber.* **1935**, *68B*, 113–120; (b) Brydowna, W. *Rocz. Chem.* **1934**, *14*, 304–325.
13. Bobbio, C.; Schlosser, M. *J. Org. Chem.* **2005**, *70*, 3039–3045.
14. Vanden eynde, J. J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 6511–6516.