Tetrahedron 66 (2010) 8000–8005

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new phenylpyridyl scaffolds using the Garlanding approach

Anne Sophie Voisin-Chiret [a], Marilena Muraglia [b], Grégory Burzicki [a], Serge Perato [a], Filomena Corbo [b], Jana Sopková-de Oliveira Santos [a], Carlo Franchini [b], Sylvain Rault [a,*]

[a] University of Caen Basse-Normandie, U.F.R. des Sciences Pharmaceutiques, Centre d'Etudes et de Recherche sur le Médicament de Normandie, UPRES EA-4258, FR CNRS INC3M, boulevard Becquerel, 14032 Caen Cedex, France
[b] University of Bari, Department of Pharmaceutical Chemistry, Via E. Orabona n.4, 70125 Bari, Italy

ARTICLE INFO

Article history:
Received 7 July 2010
Received in revised form 29 July 2010
Accepted 5 August 2010
Available online 12 August 2010

Keywords:
Boron
Cross-coupling
Palladium
Pyridines
Regioselectivity

ABSTRACT

One-pot reaction for the synthesis of novel phenylpyridyl derivatives and mixed quater phenylpyridyl compounds is described by using the Garlanding approach. The reactions proceed with moderate to good yields in mild conditions and good reaction times. This work represents a second application of the simplicity and versatility of Garlanding concept for the construction of new phenylpyridyl scaffolds, which can be considered as non-peptidic foldamer α-helix mimetics.

© 2010 Published by Elsevier Ltd.

1. Introduction

There has been a recent surge in the development of conjugated structure synthesis because of their frequency in organic and microelectronic devices such as LEDs, FETs, and solar cells.[1] Oligopyridines, mainly bi-, ter-, and quater-pyridines have also attracted strong interest and been the subject of many recent papers by reason of their ability to complex with transition metals and for their luminescence properties.[2] Beyond this application, oligopyridines can be considered as non-peptidic foldamer α-helix mimetics as well as 3,2′,2″-tris-substituted terphenyl derivatives described by Hamilton and Cummings.[3] To date, these terphenyl templates are the most well-studied and diverse set of α-helix mimetics based on protein secondary structures,[4] which will furnish potent disruptors of protein–protein interactions. For example, terpyridines have been extensively studied as DNA binding agents.[5]

Despite of their great interest more detailed synthetic strategies seem to be required for revealing an efficient approach to obtain oligopyridyl isomer derivatives.

Here, as a continuation of our recent studies involving the preparation of various bi-, ter-, and quater-pyridines using iterative cross-coupling reactions,[6,7] we would like to report the utility of our experience to rapidly create several such structures with the phenylpyridyl skeleton.

The chemical strategy we used, that we named Garlanding concept (Scheme 1),[6] highlights the importance both of the regioselective control in the coupling reaction and of the choice of the coupling partners. Indeed, this methodology takes advantage of the nature as well as of the position of the halogen atom on the ring. In addition, it uses bifunctional (hetero)arylboronic acids, which represent a highly promising platform for this type of synthetic strategy.

To study the feasibility and the repeatability of the reaction and to show the efficiency of the Garlanding concept a first series of compounds (bi-, ter-, and quater-pyridines) was prepared.[7]

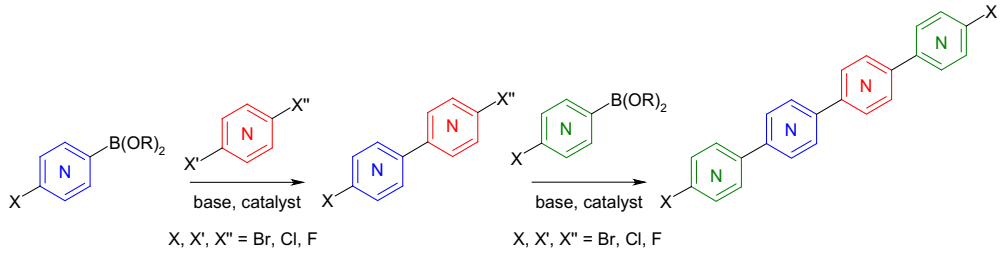
Since the Garlanding concept has demonstrated an efficient and a good reaction time, so as a high flexibility in order to couple selectively each halogen, we envisioned that it may be employed for the synthesis of mixed phenylpyridyl compounds.

Several reasons led us to study the synthesis of such a series.

- Firstly, to show the useful extension of the Garlanding approach, we studied the reactivity of other coupling partners as phenyl compounds in the preparation of novel phenylpyridines.
- Secondly, we also carried out the synthesis of novel mixed quater phenylpyridyl derivatives to explore the reactivity of the new generated chemical intermediates phenylpyridines.
- Thirdly, we aimed to grasp the chemical arrangement (reagents and conditions) due to the replacement of pyridine rings by phenyl.

* Corresponding author. Tel.: +33 231 56 6801; fax: +33 231 56 6803; e-mail address: sylvain.rault@unicaen.fr (S. Rault).

0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.08.008

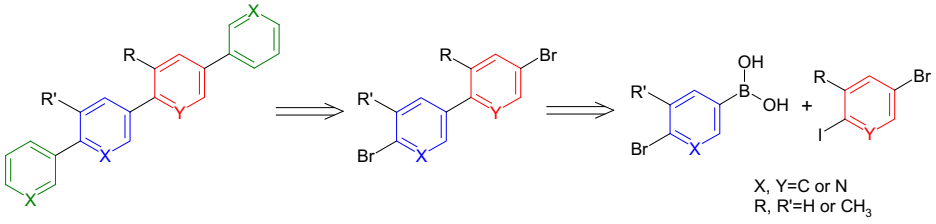


Scheme 1. The Garlanding concept.

- Fourthly, in this preliminary study we planned to investigate how the steric hindrance, due to a little moiety so as a methyl group, can modulate the Garlanding approach.

All obtained structures are summarized in Tables 1 and 2. A plausible mechanism of the explored reaction is reported in Scheme 2.

2-Bromo-5-(4-bromophenyl)pyridine **3a**, 2-bromo-5-(4-bromo-2-methylphenyl)-3-methylpyridine **3b**, 5-bromo-2-(4-bromophenyl) pyridine **3c**, and 5-bromo-2-(4-bromo-3-methylphenyl)-3-methylpyridine **3d** were synthesized with 60%, 30%, 46%, and 63% yields, respectively (Table 1). At the beginning of our research program, three phenylpyridines **3a**,[10] **3b**, and **3d** were novel and phenylpyridine **3c**

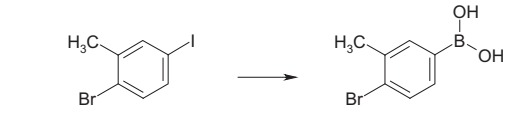


Scheme 2. General procedure to prepare phenylpyridyl and mixed quater phenylpyridyl compounds.

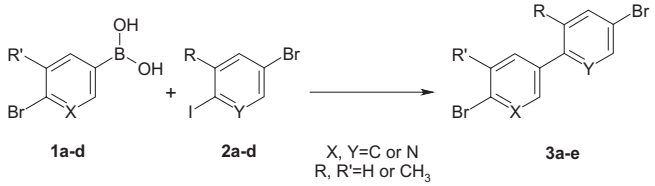
2. Results

During our ongoing investigation, we first examined the reactivity of the coupling partners with the preparation of phenylpyridines **3a**–**d** obtained by the cross-coupling reaction between halogenated boronic acids **1a**–**d** and halides **2a**–**d** as illustrated in Scheme 4.

Among the generated boronic acid, 4-bromo-3-methylphenyl boronic acid **1d** was known because registered in a patent that suggest the synthesis of the cited compound starting by a tetrahydroxyboron, previously isolated.[8] Anyway, no experimental data were depicted. In order to prepare and characterize compound **1d**, we used our laboratory expertise in the synthesis of boronic species:[9] one-pot reaction starting with 1-bromo-4-iodo-2-methylbenzene, commercially available, by proceeding through the reactive organolithium intermediate, generated by a regioselective halogen–lithium exchange, afforded the desired compound in a very good yield (77%) (Scheme 3).

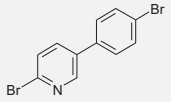
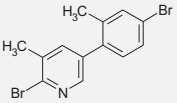
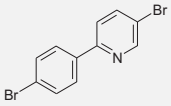
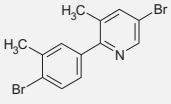
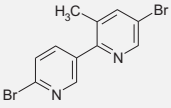


Scheme 3. Synthesis of 4-bromo-3-methylphenyl boronic acid **1d**. Reagents and conditions: (1) *n*-BuLi, 1.25 equiv, THFanhyd, −78 °C, 1.5 h; (2) B(O*i*-Pr)$_3$, 1.25 equiv, THFanhyd, −78 °C, 1 h then rt; (3) hydrolysis.



Scheme 4. Preparation of compounds **3a**–**e**. Reagents and conditions: boronic acid **1a**–**d** 1.1 equiv, halide **2a**–**d** 1 equiv, Na_2CO_3aq 2.5 equiv, $Pd(PPh_3)_4$ 0.04 equiv, 1,4-dioxane, reflux, 24 h.

Table 1
Cross-coupling reactions between halogenated boronic acids **1a**–**d** and halides **2a**–**d**

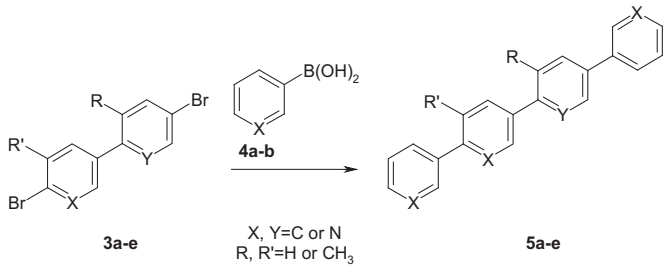
	Boronic acid			Halide		Phenylpyridine/Bipyridine		
	X	R′		Y	R			Yield (%)
1a	N	H	**2c**	C	H		**3a**	60
1b	N	CH_3	**2d**	C	CH_3		**3b**	30
1c	C	H	**2a**	N	H		**3c**	46
1d	C	CH_3	**2b**	N	CH_3		**3d**	63
1a	N	H	**2b**	N	CH_3		**3e**	86

was known[11] for its optical[12] and luminescence properties[13] and as phosphorescent devices.[14]

In order to study the versatility of our suggested synthetic approach so as to compare the reactivity of coupling partners, we reminded of the preparation of 5,6′-dibromo-3-methyl-2,3′-bipyridine **3e** starting from 6-bromo-pyridin-3-yl boronic acid **1a** and 5-bromo-2-iodo-3-methylpyridine **2b**, which was obtained with excellent yield (86%) as other analogous mono-or di-methylated dibromobipyridines previously reported.[7a]

By comparison the results reported in Table 1, it is worthy to note that **3a**–**d** yields are surprisingly lower than **3e** yield. These evidences led us to think that the difference of yields is probably due to homocoupling side reactions leading to the production of a small amount of biphenylpyridines. In fact, traces of biphenylpyridyl derivatives were detected by ^{1}H NMR and MS analysis.

In the second part of this study, we explored the reactivity of phenylpyridines **3a**–**d** and bipyridine **3e** bearing two bromine atoms essential to the elongation of the garland. These five compounds were involved in coupling reactions with pyridin-3-yl boronic acid **4a** and phenyl boronic acid **4b** (Scheme 5).



Scheme 5. Preparation of compounds **5a**–**e**. Reagents and conditions: boronic acid **4a**,**b**, halide **3a**–**e**, Na_2CO_3aq, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 24 h.

Despite the difference in the reactivity of two bromine atoms, one in the alpha position of the pyridine nitrogen and the other in beta position, the presence of boronic acids in slight excess allowed the synthesis of five novel mixed quater phenylpyridyl compounds: 5-(4-pyridin-3-ylphenyl)-2,3′-bipyridine **5a**, 3-methyl-5-(2-methyl-4-pyridin-3-ylphenyl)-2,3′-bipyridine **5b**, 6-(4-pyridin-3-ylphenyl)-3,3′-bipyridine **5c**, 5-methyl-6-(3-methyl-4-pyridin-3-ylphenyl)-3,3′-bipyridine **5d**, and 3-methyl-5,6′-diphenyl-2,3′-bipyridine **5e**.

All desired compounds were prepared through a one-pot reaction and products were isolated after chromatography in good yields (**5a**: 41%; **5b**: 63%; **5c**: 60%; **5d**: 58%; **5e**: 80%; **5f**: 73%) as stable solids (Table 2).

Surprisingly, the coupling reaction to obtain 3-methyl-5,6′-diphenyl-2,3′-bipyridine **5e** was more efficient (80% yield) if compared to the yields of other compounds (**5a**–**d**). At the light of these results we may think that phenyl boronic acid **4b** is a more suitable coupling partner because of less sensitive to the protodeboronation than pyridin-3-yl boronic acid **4a**.

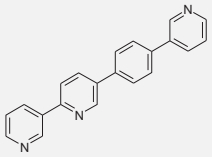
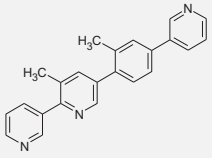
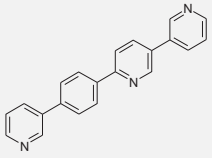
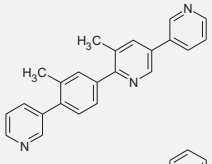
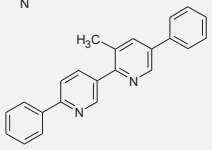
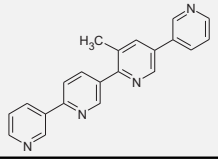
Then, to confirm this hypothesis we also attempted the preparation of its analogue 3″-methyl-3,2′:5′,2″:5″,3′-quaterpyridine **5f** from the same intermediate **3e** in the presence of pyridylboronic acid **4a**, under the same condition reaction. It was synthesized in 73% yield. Therefore, according to this result, we cannot just attribute this yield decrease to the lower stability of pyridylboronic acid **4a**. But, in contrast, phenylpyridyl intermediates **3a**–**d** are presumably less good coupling partners, more sensitive to homocoupling side reactions.

The structures of new generated compounds were unequivocally established by the usual spectroscopic means as reported in the Experimental section. Detail of the successfully reactions are reported in this paper.

Finally, because terpyridines has been studied as DNA binding agents[5] and taking into account that a careful screening of the literature describes very few cytotoxic effects of olygopyridyl derivatives, all compounds described in this paper were preliminary screened for a potential cytotoxic activity by an in vitro assay of growth inhibition against KB cells.

In general, the obtained results suggest that the compounds did not produce a relevant change in cell viability in KB cells (none of them shows a cytotoxic activity on KB cells at 10^{-5} M). These data will furnish very valuable information in the context of the exploration of biological properties study of perturbations of protein–protein interactions and further investigations will be carry on to explore their biological properties and their ability to mimic α-helix.

Table 2
Cross-coupling reactions between boronic acids **4a**,**b** and phenylpyridine/bipyridine **3e**,**f**

Phenylpyridine / bipyridine	Mixed quater phenylpyridyl	Compound	Yield (%)
3a		**5a**	41
3b		**5b**	63
3c		**5c**	60
3d		**5d**	58
3e		**5e**	80
3e		**5f**	73

3. Conclusion

In summary, we have successfully applied the efficient, feasibility and versatility of the Garlanding concept through the construction of new phenylpyridyl scaffolds. In particular, we developed a one-pot reaction to obtain three novel phenylpyridyl derivatives and six new mixed quater phenylpyridyl compounds. The reactions proceeded smoothly in moderate to good yields. In the light of the majority of experimental findings we strongly suggest that phenylpyridyl intermediates (**3a**–**d**) are not good coupling partners by considering their more sensitive to homocoupling side reactions.

Then, on the basis of the results presented in this work, further applications and investigations of the Garlanding approach in the field of mechanistic and synthetic organic chemistry as well as in biological area are currently going on in our laboratory.

4. Experimental section

4.1. General procedure

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler heating bench.

IR spectra were recorded on a Perkin–Elmer BX FT-IR spectrophotometer. The band positions are given in reciprocal centimeters (cm^{-1}).

Compounds **3a**–**c**, **3e**, **5e**–**f** ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. Compounds **1d**, **3d**, and **5a**–**d** ^{1}H NMR (300 MHz) were recorded on a FT Bruker Aspect 3000 spectrometer (Bruker Bioscience, USA) and **1d**, **3d**, and **5a**–**d** ^{13}C NMR (75 MHz) were recorded on a Varian Mercury 300 NMR spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants in hertz. Chemical shift are reported in part per million (ppm) relative to the solvent resonance.

Compounds **5e**,**f** mass spectra were recorded on a JEOL JMS GCMate spectrometer at ionizing potential of 70 eV (EI) and with pfk as internal standard for high-resolution procedure, or were performed using a spectrometer LC–MS Waters alliance 2695 (ESI^+).

Compounds **1d**, **3a**–**d**, and **5a**–**d** EIMS spectra were recorded with a Helwett–Packard 6890–5973 MSD gas chromatograph/mass spectrometer at low resolution (Helwett–Packard, Palo Alto, CA, USA).

Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. The eluting solvent indicated for each purification was determined by thin layer chromatography (TLC) performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck) and spots were visualized using an ultraviolet-light lamp.

Compounds **1d**, **3a**–**d**, and **5a**–**d** elemental analysis were performed on a Eurovector Euro EA 3000 elemental analyzer (euroVector, Milan, Italy). The data for C, H, and N were within ±0.4 of the theoretical values for all final compounds.

4.2. 4-Bromo-3-methylphenyl boronic acid 1d

To a 2.5 M solution of *n*-BuLi (1.25 equiv, 11.8 mL, 29.4 mmol) in anhydrous THF, cooled to −78 °C was added dropwise a solution of 1-bromo-4-iodo-2-methylbenzene (1 equiv, 7 g, 23.4 mmol) in anhydrous THF. The resulting mixture was allowed to react at this temperature for over 1.5 h. A solution of triisopropylborate (1.25 equiv, 7 mL, 29.4 mmol) in anhydrous THF was then dropwise added, keeping the internal temperature at −78 °C. The mixture was allowed to warm to room temperature and left to react for an additional hour. The resulting mixture was quenched by slow addition of 3 N HCl. Extraction with ethyl acetate, evaporation of the organic layer and crystallization from CH_3CN afforded pure 4-bromo-3-methylphenyl boronic acid **1d** as a pale white solid (3.9 g, 77%). Mp >250 °C (CH_3CN). IR (KBr): 3434, 1591, 1385, 1344, 1095, 1021, 735, 716 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ 8.13 (s, 2H, O*H*), 7.71 (s, 1H, *H*2), 7.53–7.47 (AB system, *J*=7.8, 2H, *H*5, *H*6), 2.33 (s, 3H C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 138–1-137.5 (m, *C*1), 137.1 (*C*2), 134.0 (*C*3), 133.6 (*C*6), 132.7 (*C*5), 127.6 (*C*4), 22.9 (*C*H_3).

4.3. General procedure for cross-coupling reactions

A mixture of boronic acid **1a**–**d** (1.1 equiv), halides **2a**–**d** (1 equiv), tetrakis(triphenylphosphine) palladium(0) (5 mol %) and aqueous Na_2CO_3 (2.5 equiv) in 1,4-dioxane was heated at 80 °C for 1 h then under reflux until the complete consumption of aryl halide (TLC). The reaction mixture was concentrated, extracted with ethyl acetate. Organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 95/5) to afford pure compounds **3a**–**e**.

Boronic acid **4a**,**b** (2.5 equiv), 1 equiv of compounds **3e**, 10 mol % tetrakis(triphenylphosphine) palladium(0), and 5 equiv aqueous Na_2CO_3 are used to afford pure compounds **5e** and **5f** by following the same condition reaction above described.

Boronic acid **4a**,**b** (3.2 equiv), 1 equiv of compounds **3a**,**b**, 15 mol % tetrakis(triphenylphosphine) palladium(0), and 7 equiv aqueous Na_2CO_3 are used to afford pure compounds **5a** and **5b**. The resulting crude products were purified by flash column chromatography using CH_2Cl_2/CH_3OH (95/5) solvent system.

Boronic acid **4a** (4.3 equiv), 1 equiv of compounds **3c**, 20 mol % tetrakis(triphenylphosphine) palladium(0), and 9.6 equiv aqueous Na_2CO_3 are used to afford pure compounds **5c**. The resulting crude products were purified by flash column chromatography using CH_2Cl_2/CH_3OH (98/2) solvent system.

4.4. 2-Bromo-5-(4-bromophenyl)pyridine 3a

Starting from 6-bromo-pyridin-3-yl boronic acid **1a** (1.6 g, 7.8 mmol) and 1-bromo-4-iodobenzene **2c** (2 g, 7.0 mmol) and following the general procedure, the product **3a** was obtained as a yellow solid (1.32 g, 60%). Mp 143 °C. IR (KBr): 1574, 1449, 1400, 1351, 1085, 994, 809, 682, 547 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J*=2.0, 1H, *H*6), 7.70 (dd, *J*=2.0, 7.8, 1H, *H*4), 7.61 (d, *J*=8.8, 2H, *H*2′, *H*6′), 7.55 (d, *J*=7.8, 1H, *H*3), 7.41 (d, *J*=8.8, 2H, *H*3′, *H*5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2 (C6), 141.3 (C2), 136.7 (C5), 135.4 (C4′), 134.9 (C4), 132.4 (C2′, C6′), 128.5 (C3′, C5′), 128.1 (C3), 123.0 (C1′). MS (EI): *m*/*z* (%)=312 (M^+,53); 314 (M^++2, 100); 316 (M^++4, 49). Anal. Calcd for $C_{11}H_7NBr_2 \cdot 0.33H_2O$: C, 41.42; H, 2.42; N, 4.39. Found: C, 41.15; H, 2.09; N, 4.16.

4.5. 2-Bromo-5-(4-bromo-2-methylphenyl)-3-methyl pyridine 3b

Starting from 6-bromo-5-methyl-pyridin-3-yl boronic acid **1b** (1.6 g, 7.5 mmol) and 5-bromo-2-iodotoluene **2d** (2 g, 6.8 mmol) and following the general procedure, the product **3b** was obtained as a white solid (0.7 g, 30%). Mp 117 °C. IR (KBr): 1585, 1540, 1451, 1394, 1057, 993, 820, 736, 666, 559 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J*=2.0, 1H, *H*6), 7.45–7.44 (m, 2H, *H*4, *H*3′), 7.40 (dd, *J*=1.9, 8.8, 1H, *H*5′), 7.04 (d, *J*=8.8, 1H, *H*6′), 2.44 (s, 3H, C*H*$_3$–ph), 2.26 (s, 3H, C*H*$_3$–py). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1 (*C*6), 143.5 (*C*2), 139.1 (*C*3), 137.7 (*C*5), 135.8 (*C*4), 135.7 (*C*2′), 134.7 (*C*6′), 133.4 (*C*5′), 131.2 (*C*3′), 129.3 (*C*1′), 122.3 (*C*4′), 22.0 (*C*H_3–ph), 20.2 (*C*H_3–py). MS (EI): *m*/*z* (%)=339 (M^+, 53); 341 (M^++2, 100); 343 (M^++4, 49). Anal. Calcd for $C_{13}H_{11}NBr_2$: C, 45.78; H, 3.25; N, 4.11. Found: C, 45.65; H, 3.19; N, 4.17.

4.6. 5-Bromo-2-(4-bromophenyl)pyridine 3c

Starting from 4-bromo-benzene boronic acid **1c** (1.56 g, 7.74 mmol) and 3-bromo-6-iodopyridine **2a** (2 g, 7.04 mmol) and following the general procedure, the product **3c** was obtained as a white solid (1.012 g, 46%). Mp 125 °C. Same experimental data described in the literature.[11]

4.7. 5-Bromo-2-(4-bromo-3-methylphenyl)-3-methyl pyridine 3d

Starting from 4-bromo-3-methylphenyl boronic acid **1d** (0.860 g, 4 mmol) and 3-bromo-5-methyl-6-iodopyridine **2b** (1.077 g, 3.62 mmol) and following the general procedure, the product **3d** was obtained as a pale white solid (0.775 g, 63%). Mp 105 °C. IR (KBr): 1571, 1542, 1452, 1420, 1029, 892, 821, 697, 549 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, *J*=1.9, 1H, *H*6), 7.73 (d, *J*=1.9, 1H, *H*4), 7.59 (d, *J*=8.0, 1H, *H*5′), 7.37 (d, *J*=1.9, 1H, *H*2′), 7.16 (dd, *J*=1.9, 8.0, 1H, *H*6′), 2,45 (s, 3H, C*H*$_3$–ph), 2.33 (s, 3H, C*H*$_3$–py). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4 (*C*2), 148.2 (*C*6), 141.1 (*C*4), 138.9 (*C*5), 138.3 (*C*4′), 132.9 (*C*1′), 132.4 (*C*6′), 131.5 (*C*2′), 127.9 (*C*5′), 125.3

(*C*3), 119.4 (*C*3′), 23.2 (*C*H$_3$–ph), 20.1 (*C*H$_3$–py). MS (EI): *m*/*z* (%)=338 (M$^+$, 52); 340 (M$^+$+2, 100); 343 (M$^+$+4, 53). Anal. Calcd for $C_{13}H_{11}NBr_2 \cdot H_2O$: C, 43.49; H, 3.65; N, 3.90. Found: C, 43.11; H, 3.52; N, 4.02.

4.8. 5,6′-Dibromo-3-methyl-2,3′-bipyridine 3e

Starting from 6-bromo-pyridin-3-yl boronic acid **1a** (1.66 g, 8.22 mmol) and 3-bromo-5-methyl-6-iodopyridine **2b** (2.00 g, 6.71 mmol) and following the general procedure, the product **3e** was obtained as a yellow solid (1.90 g, 86%). Mp 150 °C. Same experimental data described in the literature.[7a]

4.9. 5-(4-Pyridin-3-ylphenyl)-2,3′-bipyridine 5a

Starting from pyridin-3-yl boronic acid **4a** (0.629 g, 5.12 mmol) and 2-bromo-5-(4-bromophenyl)pyridine **3a** (0.500 g, 1.6 mmol) and following the general procedure, the product **5a** was obtained as a pale yellow solid (0.202 g, 41%). Mp 170 °C (CH_3OH). IR (KBr): 1592, 1574, 1463, 1189, 1010, 803, 706, 558 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.27 (d, *J*=1.9, 1H, *H*2′), 9.02 (d, *J*=1.9, 1H, *H*6), 8.92 (d, *J*=1.9, 1H, *H*2‴), 8.68 (dd, *J*=1.4, 4.7, 1H, *H*6′), 8.64 (dd, *J*=1.4, 4.7, 1H, *H*6‴), 8.41 (dt, *J*=1.9, 8.0, 1H, *H*4′), 8.06 (dd, *J*=2.2, 8.2, 1H, *H*4), 7.95 (dt, *J*=1.9, 8.0, 1H, *H*4‴), 7.88 (d, *J*=8.3, 1H, *H*3), 7.79–7.72 (m, 4H, *H*2″, *H*3″, *H*5″, *H*6″), 7.48–7.40 (m, 2H, *H*5′, *H*5‴). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (*C*2), 150.3 (*C*2‴), 149.1 (*C*6′), 148.6 (*C*2′), 148.5 (*C*6), 148.4 (*C*6‴), 138.0 (*C*1″), 137.3 (*C*4″), 136.1 (*C*3‴), 135.4 (2C, *C*4′, *C*4‴), 135.2 (*C*3′), 134.6 (*C*5), 134.4 (*C*5′, *C*5‴), 128.1 (*C*3″, *C*5″), 127.9 (*C*2″, *C*6″), 129.3 (*C*4), 120.7 (*C*3). MS (EI): *m*/*z* (%)=309 (M$^+$, 100). Anal. Calcd for $C_{21}H_{15}N_3.1/3H_2O$: C, 79.98; H, 5.01; N, 13.32. Found: C, 80.27; H, 4.85; N, 13.01.

4.10. 3-Methyl-5-(2-methyl-4-pyridin-3-ylphenyl)-2,3′-bipyridine 5b

Starting from pyridin-3-yl boronic acid **4a** (0.300 g, 3.74 mmol) and 2-bromo-5-(4-bromo-2-methylphenyl)-3-methyl pyridine **3b** (0.400 g, 1.17 mmol) and following the general procedure, the product **5b** was obtained as a pale yellow solid (0.248 g, 63%). Mp 110 °C (CH_3OH/Et_2O). IR (KBr): 1573, 1464, 1414, 1380, 1011, 800, 709, 607 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.91 (d, *J*=1.9, 1H, *H*2′), 8.89 (d, *J*=1.9, 1H, *H*6), 8.68 (dd, *J*=1.9, 4.7, 1H, *H*6‴), 8.63 (d, *J*=3.8, 1H, *H*4′), 8.59 (d, *J*=1.9, 1H, *H*2‴), 8.00–7.92 (m, 2H, *H*4′, *H*4), 7.64 (d, *J*=1.9, 1H, *H*4‴), 7.54–7.38 (m, 5H, H5′, *H*5‴, *H*6″, *H*5″, *H*3″), 2,47 (s, 3H, C*H*$_3$–ph), 2.43 (s, 3H, C*H*$_3$–py). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2 (*C*2), 150.1 (*C*6′), 149.2 (*C*2‴), 148.7 (*C*2′), 148.3 (*C*6), 147.7 (*C*6‴), 139.5 (*C*2″), 137.9 (*C*5), 137.5 (*C*3′), 136.9 (*C*4′), 136.8 (*C*4), 136.4 (*C*3‴), 136.2 (*C*3, *C*5′), 134.7 (*C*5‴), 131.0 (*C*4′), 130.9 (*C*6″), 129.6 (*C*5″), 125.1 (*C*3″), 123.9 (*C*1″), 123.5 (*C*4″), 20.6 (*C*H$_3$–ph), 20.0 (*C*H$_3$–py). MS (EI): *m*/*z* (%)=337 (M$^+$, 50); 336 (100). Anal. Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.75; H, 5.85; N, 12.33.

4.11. 6-(4-Pyridin-3-ylphenyl)-3,3′-bipyridine 5c

Starting from pyridin-3-yl boronic acid **4a** (1.014 g, 8.25 mmol) and 5-bromo-2-(4-bromophenyl)pyridine **3b** (0.600 g, 1.92 mmol) and following the general procedure, the product **5c** was obtained as a white solid (0.356 g, 60%). Mp 201 °C (CH_3OH). IR (KBr): 1586, 1467, 1422, 11,188, 1026, 798, 710, 615 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.96–8.93 (m, 3H, *H*2′, *H*2‴, *H*2), 8.67–8.63 (m, 2H, *H*6′, *H*6‴), 8.19 (d, *J*=8.3, 2H, *H*2″, *H*4‴), 8.02–7.90 (m, 4H, *H*4, *H*5, *H*3″, *H*5″), 7.74 (d, *J*=8.3, 2H, *H*6″, *H*4′), 7.47–7.41 (m, 2H, *H*5′, *H*5‴). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5 (*C*6), 149.5 (*C*6′), 149.0 (*C*6‴), 148.5 (*C*2‴), 148.3 (*C*2, *C*2′), 138.9 (*C*4), 138.6 (*C*4′), 136.2 (*C*3), 135.4 (*C*4‴), 134.5 (*C*5), 134.4 (*C*5′), 133.5 (*C*3′), 132.2 (*C*3‴), 127.8 (*C*2″, *C*3″, *C*5″, *C*6″), 124.0 (*C*4″), 123.8 (*C*1″), 120.7 (*C*5‴). MS (EI): *m*/*z* (%)=309 (M$^+$, 100). Anal. Calcd for $C_{21}H_{15}N_3$ $0.7H_2O$: C, 78.48; H, 5.12; N, 13.08. Found: C, 78.63; H, 5.46; N, 13.33.

4.12. 5-Methyl-6-(3-methyl-4-pyridin-3-ylphenyl)-3,3′-bipyridine 5d

Starting from pyridin-3-yl boronic acid **4a** (0.580 g, 4.7 mmol) and 2-bromo-5-(4-bromophenyl)pyridine **3d** (0.500 g, 1.47 mmol) and following the general procedure, the product **5d** was obtained as a yellow oil (0.290 g, 58%). IR (KBr): 1581, 1550, 1463, 1159, 981, 686, 551 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.68 (s, 1H, *H*2′), 8.56 (d, *J*=4.9, 1H, *H*6′), 8.55 (s, 1H, *H*2), 8.46 (s, 1H, *H*2‴), 8.44 (d, *J*=4.9, 1H, *H*6‴), 8.42 (d, *J*=8.2, 1H, *H*5″), 7.74 (d, *J*=7.8, 1H, *H*4′), 7.6 (d, *J*=7.8, 1H, *H*4‴), 7.41 (s, 1H, *H*4), 7.3 (dd, *J*=7.8, 4.9, 1H, *H*5′), 7.14 (dd, *J*=7.8, 4.9, 1H, *H*5‴), 7.12 (d, *J*=8.2, 1H, *H*6″), 6.79 (s, 1H, *H*2″), 2.7 (s, 3H, C*H*$_3$–ph), 2.37 (s, 3H, C*H*$_3$–py). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.65 (*C*6), 148.5 (*C*2″), 147.6 (*C*6′, C2′), 146 (*C*6″), 144 (*C*1″), 142 (*C*5), 141.3 (*C*3″), 141.1 (*C*2), 139 (*C*3‴), 137.8 (*C*4″), 133.2 (*C*4‴), 132.9 (*C*2″), 132.6 (*C*4, *C*4′), 130.9 (*C*3′), 130.1 (*C*3), 127 (*C*6″), 122.3 (*C*5′), 121 (*C*5‴), 120.5 (*C*5″), 20.75 (*C*H$_3$–ph), 20.12 (*C*H$_3$–py). MS (EI): *m*/*z* (%)=337 (M$^+$, 50); 336 (100). Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.52; H, 5.85; N, 12.11.

4.13. 3-Methyl-5,6′-diphenyl-2,3′-bipyridine 5e

Starting from phenyl boronic acid **4b** (0.371 g, 3.04 mmol) and 5,6′-dibromo-3-methyl-2,3′-bipyridine **3e** (0.400 g, 1.22 mmol) and following the general procedure, the product **5c** was obtained as a white solid (0.315 g, 80%). Mp 141 °C. IR (KBr): 3434, 1588, 1448, 1360, 902, 847, 770, 740, 694, 532 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, *J*=2.0, 1H, *H*2′), 8.81 (d, *J*=2.0, 1H, *H*6), 8.07 (d, *J*=7.8, 2H, *H*2″, *H*6″), 8.04 (dd, *J*=2.0, 7.8, 1H, *H*4′), 7.86 (d, *J*=7.8, 1H, *H*5′), 7.83 (d, *J*=2.0, 1H, *H*4), 7.65 (d, *J*=7.8, 2H, *H*2‴, *H*6‴), 7.51 (t, *J*=7.8, 4H, *H*3″, *H*5″, *H*3‴, *H*5‴), 7.46–7.43 (m, 2H, *H*4″, *H*4‴), 2.53 (s, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (*C*6′), 154.1 (*C*2), 149.8 (*C*2′), 145.9 (*C*6), 139.0 (*C*1″), 137.4 (*C*4′), 137.2 (*C*4), 135.6 (*C*5 or *C*1‴), 134.3 (*C*3′), 131.1 (*C*3), 129.1 (*C*3″, *C*5″, *C*3‴, *C*5‴), 128.8 (*C*4″, *C*4‴), 128.2 (*C*5 or *C*1‴), 127.3 (*C*2‴, *C*6‴), 127.1 (*C*2″, *C*6″), 120.0 (*C*5′), 20.2 (*C*H$_3$). MS (EI): *m*/*z* (%)=323 (100) [M+1]$^+$. HRMS (EI) *m*/*z* calcd: 322.14625, found: 322.14699. Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.31; H, 5.31; N: 8,85.

4.14. 3″-Methyl-3,2′:5′,2″:5″,3‴-quaterpyridine 5f

Starting from pyridin-3-yl boronic acid **4a** (0.297 g, 2.41 mmol) and 5,6′-dibromo-3-methyl-2,3′-bipyridine **3e** (0.305 g, 0.93 mmol) and following the general procedure, the product **5c** was obtained as a white solid (0.315 g, 80%). Mp 156 °C. IR (KBr): 1591, 1577, 1465, 1414, 1378, 1367, 1190, 1013, 800, 771, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (d, *J*=2.0, 1H, *H*6′), 8.98 (d, *J*=2.0, 1H, *H*6″), 8.92 (d, *J*=2.0, 1H, *H*2‴), 8.82 (d, *J*=2.0, 1H, *H*2), 8.70 (d, *J*=4.9, 2H, *H*6, *H*6‴), 8.42 (dt, *J*=2.0, 7.8, 1H, *H*4), 8.09 (dd, *J*=2.0, 7.8, 1H, *H*4′), 7.95 (dt, *J*=2.0, 7.8, 1H, *H*4‴), 7.91 (d, *J*=7.8, 1H, *H*3′), 7.86 (d, *J*=2.0, 1H, *H*4″), 7.45 (dd, *J*=4.9, 7.8, 2H, *H*5, *H*5‴), 2.56 (s, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6 (*C*2′), 154.2 (*C*2″), 150.1 (*C*2), 150.0 (*C*6), 149.4 (*C*6‴), 148.3 (*C*6″), 148.1 (*C*2‴), 145.7 (*C*6′), 137.6 (*C*4′), 137.2 (*C*4″), 134.7 (*C*5′), 134.4 (*C*3), 134.3 (*C*4, *C*4‴), 132.9 (*C*5″), 132.5(*C*3‴), 131.5 (*C*3″), 123.7 (*C*5), 123.6 (*C*5‴), 120.0 (*C*3′), 20.1 (*C*H$_3$). MS (EI): *m*/*z* (%)=112 (100), 325 (12) [M+1]$^+$. HRMS (EI) *m*/*z* calcd: 324.13748, found: 324.13658. Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.49; H, 4.61; N: 17.61.

Acknowledgements

We thank Dr. Thierry Cresteil of the 'Institut de Chimie des Substances Naturelles' for cytotoxic activity evaluations.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.008.

References and notes

1. Dutta, T.; Woody, K. B.; Parkin, S. R.; Watson, M. D.; Gierschner, J. *J. Am. Chem. Soc.* **2009**, *131*, 17321–17327.
2. (a) Constable, E. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2748–2749; (b) Constable, E. C. *Prog. Inorg. Chem.* **1994**, *42*, 67–138; (c) Constable, E. C. *Adv. Inorg. Chem.* **1986**, *30*, 69–121; (d) Fang, Y. Q.; Polson, M. I. J.; Hanan, G. S. *Inorg. Chem.* **2003**, *42*, 5–7.
3. (a) Cummings, C. G.; Hamilton, A. D. *Curr. Opin. Chem. Biol.* **2010**, *14*, 341–346; (b) Orner, B. P.; Ernst, J. T.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 5382–5383.
4. Davis, J. M.; Tsou, L. K.; Hamilton, A. D. *Chem. Soc. Rev.* **2007**, *36*, 326–334.
5. Zhao, L. X.; Kim, T. S.; Ahn, S. H.; Kim, T. H.; Kim, E. K.; Cho, W. J.; Choi, H.; Lee, C. S.; Kim, J. A.; Jeong, T. C.; Chang, C. J.; Lee, E. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2659–2662.
6. Voisin-Chiret, A. S.; Bouillon, A.; Burzicki, G.; Célant, M.; Legay, R.; El-Kashef, H.; Rault, S. *Tetrahedron* **2009**, *65*, 607–612.
7. (a) Burzicki, G.; Voisin-Chiret, A. S.; Sopkovà-de Oliveira Santos, J.; Rault, S. *Tetrahedron* **2009**, *65*, 5413–5417; (b) Burzicki, G.; Voisin-Chiret, A. S.; Sopkovà-de Oliveira Santos, J.; Rault, S. *Synthesis* **2010**, *16*, 2804–2810.
8. (a) Ohmori, Y.; Komatsu, M. PCT Int. Appl. WO 2008023783 A1 20080228, 2008. (b) Aono, K.; Ichihashi, T.; Kugimiya, A. PCT Int. Appl. WO 2001005768 A1 20010125, 2001; (c) Marcuccio, S.M.; Rodopoulos, M.; Weigold, H. PCT Int. Appl. WO 9912940 A1 19990318, 1999.
9. (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; (d) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049; (e) Voisin, A. S.; Bouillon, A.; Berenguer, I.; Lancelot, J. C.; Lesnard, A.; Rault, S. *Tetrahedron* **2006**, *62*, 11734–11739; (f) Cailly, T.; Fabis, F.; Bouillon, A.; Lemaître, S.; Sopková-de Olivieira Santos, J.; Rault, S. *Synlett* **2006**, 53–56.
10. Commercially available (Acentex Scientific, Inc), but its synthesis is unknown in the literature.
11. Thomas, S. W.; Yagi, S.; Swager, T. M. *J. Mater. Chem.* **2005**, *15*, 2829–2835.
12. (a) Langecker, J.; Rehahn, M. *Macromol. Chem. Phys.* **2008**, *209*, 258–271; (b) Venkatesan, K.; Kouwer, P. H. J.; Yagi, S.; Mueller, P.; Swager, T. M. *J. Mater. Chem.* **2008**, *18*, 400–407; (c) Yamamoto, T.; Zhou, Z.-h.; Kanbara, T.; Shimura, M.; Kizu, K.; Maruyama, T.; Nakamura, Y.; Fukuda, T.; Lee, B.-L.; Ooba, N.; Tomaru, S.; Kurihara, T.; Kaino, T.; Kubota, K.; Sasaki, S. *J. Am. Chem. Soc.* **1996**, *118*, 10389–10399; (d) Langecker, J.; Rehahn, M. *Polym. Prepr.* **2007**, *48*, 591–592.
13. (a) Grushin, V.; Petrov, V.A. PCT Int. Appl. WO 2003069961, 2003; (b) Grushin, V.; Lecloux, D.D.; Petrov, V.A.; Wang, Y. U.S. Patent Appl. 2,002,190,250, 2002; (c) Petrov, V.A.; Wang, Y.; Grushin, V. PCT Int. Appl. WO 2002002714, 2002.
14. (a) Schulz, G. L.; Holdcroft, S. *Chem. Mater.* **2008**, *20*, 5351–5355; (b) Schulz, G. L.; Chen, X.; Chen, S.-A.; Holdcroft, S. *Macromolecules* **2006**, *39*, 9157–9165; (c) Zhang, Y.; Xu, Y.; Niu, Q.; Peng, J.; Yang, W.; Zhu, X.; Cao, Y. *J. Mater. Chem.* **2007**, *17*, 992–1001.