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Tetrahedron 62 (2006) 11734–11739
Tetrahedron

Novel oxybispyridylboronic acids: synthesis and study of their reactivity in Suzuki-type cross-coupling reactions

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Received 26 July 2006; revised 24 August 2006; accepted 12 September 2006
Available online 17 October 2006

Abstract—This paper sets forth the synthesis of novel oxybispyridylboronic acids, which are prepared from the corresponding halo-oxybispyridines via halogen–metal exchange using *n*-butyllithium and treatment with triisopropylborate. A range of efficient cross-coupling reactions of these novel boronic acids with selected aryl halides is described. This strategy produces novel pyridylethers of interest in cholinergic medicinal chemistry.
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1. Introduction

Ligands of neuronal nicotinic cholinergic receptors (nAChRs) have been widely investigated[1] and several strategies applied in nAChR ligand design have been considered. But, the vast majority of nAChR ligands published to date suffer from a lack of selectivity for neuronal nAChR subtypes and design of novel nAChR ligands still remains to be studied.

We were particularly interested in 3-pyridylethers since these compounds have been previously identified to be potent ligands of the α4β2 nAChR subtype.[2]

In this study, we chose to develop the synthesis of novel pyridylethers taking RWJ-314313[2] and ABT-594[3] as examples (Fig. 1). RWJ-314313 is a neuronal nAChR ligand with nanomolar affinity for the α4β2 subtype ([^{3}H]cytisine binding, rat brain (α4β2), IC_{50}=22 nM), and ABT-594 is a potent agonist of α4β2 nAChRs ([^{3}H]cytisine binding, rat brain (α4β2), K_i=0.03 nM).

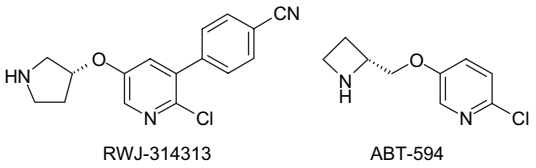
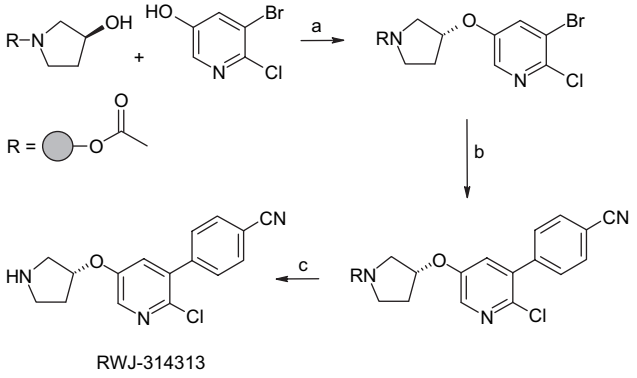


Figure 1. Nicotinic cholinergic agonists (α4β2).

These two ligands were prepared using a Mitsunobu coupling between 2-chloro-5-hydroxypyridine derivatives and appropriate *N*-protected azacycles. In the case of RWJ-314313, a Suzuki cross-coupling between pyridylether and 4-cyanophenylboronic acid provided the desired compound (Scheme 1). This synthetic strategy is limited by the availability of aryl boronic acids.



Scheme 1. Synthesis of RWJ-314313. Reagents and conditions: (a) PPh_3, DEAD, THF; (b) 4-cyanophenylboronic acid, LiCl, $Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH; (c) 95% TFA/H_2O.

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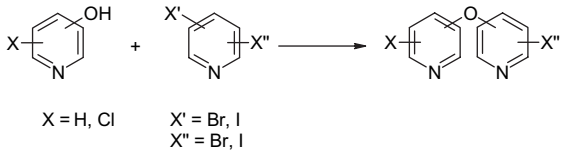
doi:10.1016/j.tet.2006.09.036

In this work, we suggested to develop an opposite strategy and to prepare boronic acid of pyridylethers in order to produce new potent pyridylethers. Moreover, this methodology seems to be more attractive insofar as numerous aryl halides are easily available.

2. Results and discussion

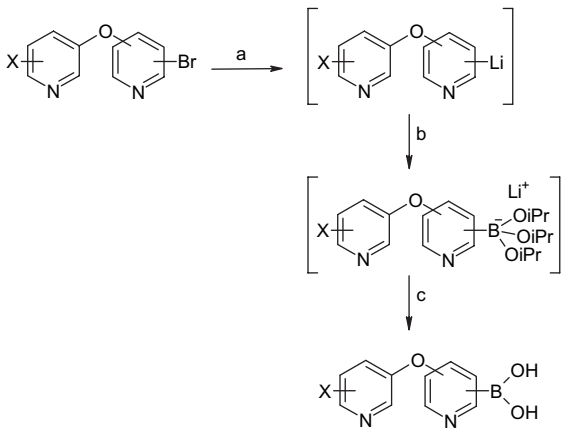
On the one hand, we recently prepared novel halo-oxybispyridines[4] from hydroxypyridines we previously published[5] (Scheme 2).



Scheme 2. Synthesis of halo-oxybispyridines. Reagents and conditions: NaH 60% (1.25 equiv), DMF, reflux, 48 h.

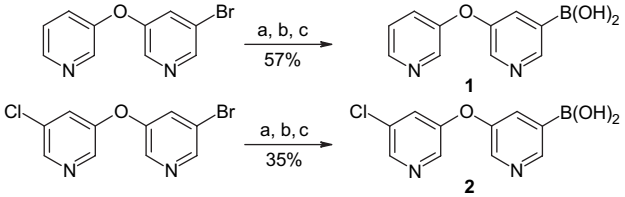
On the other hand, we described the synthesis and the isolation of halopyridylboronic acids and esters prepared taking into account a regioselective halogen–metal exchange using *n*-BuLi or a directed *ortho*-metalation using LDA.[6–9]

We report in this study the synthesis and the isolation of novel oxybispyridylboronic acids prepared via a regioselective halogen–metal exchange from the corresponding halo-oxybispyridines (Scheme 3). Bromine–lithium exchange was carried out in ether at −78 °C with *n*-BuLi, followed by the reaction with triisopropylborate B(O*i*-Pr)$_3$, then by a controlled hydrolysis.



Scheme 3. Synthesis of novel oxybispyridylboronic acids. Reagents and conditions: (a) *n*-BuLi 1.25 equiv, ether, −78 °C; (b) B(O*i*-Pr)$_3$ 1.25 equiv, −78 °C; (c) hydrolysis.

Our first attempts used 3-bromo-5-(pyridin-3-yloxy)pyridine as starting material with 1.25 equiv of *n*-BuLi. Bromine–lithium exchange was characterized by a yellow precipitate corresponding to the lithiopyridine, which then reacted with 1.25 equiv of B(O*i*-Pr)$_3$. The mixture was quenched by slow addition of 1 M aqueous NaOH solution at room temperature and the resulting aqueous layer neutralized by careful addition of HCl 6 N to prevent protodeboronation. These first conditions allowed us to obtain 5-(pyridin-3-yloxy)pyridin-3-yl boronic acid **1** with 57% yield (Scheme 4).



Scheme 4. Synthesis of novel oxybispyridylboronic acids **1** and **2**. Reagents and conditions: (a) *n*-BuLi 1.25 equiv, ether, −78 °C; (b) B(O*i*-Pr)$_3$ 1.25 equiv, −78 °C; (c) hydrolysis.

The same conditions applied to 3-bromo-5-(5-chloropyridin-3-yloxy)pyridine afforded 5-(5-chloropyridin-3-yloxy)-pyridin-3-yl boronic acid **2** (35%) (Scheme 4).

In order to generalize these conditions, we decided to prepare boronic acids of the other halo-oxybispyridines we previously synthesized, which contain pyridylether pattern in 2-position of the pyridine (Fig. 2).

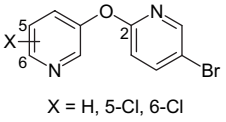


Figure 2. Halo-oxybispyridines containing pyridylether pattern in 2-position of the pyridine.

However, when using the same conditions, we did not manage to obtain the expected products. Indeed, 1 equiv of *n*-BuLi could be involved in an internal cooperating lithium complexation by both the pyridine nitrogen and pyridyloxy group as shown in Figure 3. This kind of chelation effect was already described in pyridino-directed lithiation of 2-(2-methoxyphenyl)pyridines,[10] where the cooperative internal chelation occurs with the pyridine nitrogen and methoxy group. Then, a second equivalent of *n*-BuLi could afford the corresponding boronic acids.

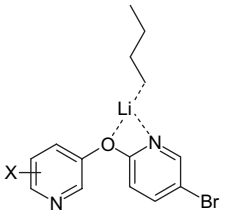
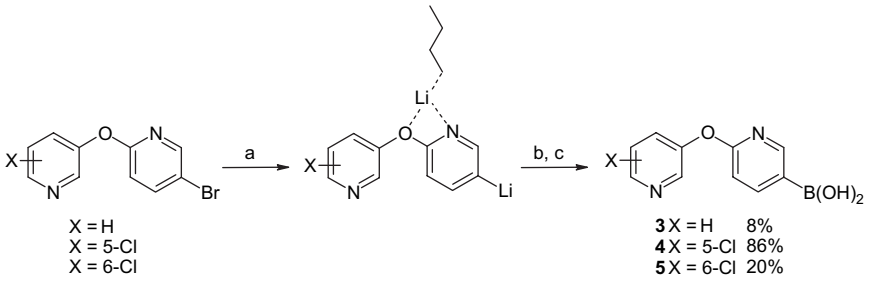


Figure 3. Proposed model for cooperative internal chelation.

Therefore, we used 2.2 equiv of *n*-BuLi and 2.2 equiv of B(O*i*-Pr)$_3$. These conditions allowed us to prepare 6-(pyridin-3-yloxy)pyridin-3-yl boronic acid **3**, 6-(5-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **4** and 6-(6-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **5** from the corresponding halo-oxybispyridines in 8%, 86% and 20% yields, respectively (Scheme 5).

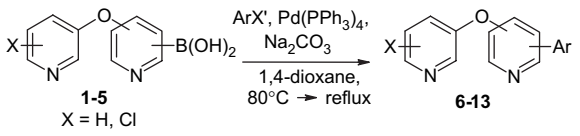
Such heterogeneous yields were surprising. Indeed, in the case of compounds **3** and **5**, boronic acids were obtained



Scheme 5. Synthesis of novel oxybispyridylboronic acids **3**–**5**. Reagents and conditions: (a) *n*-BuLi 2.2 equiv, ether, −78 °C; (b) B(O*i*-Pr)$_3$ 2.2 equiv, −78 °C; (c) hydrolysis.

with degradation products and without starting materials. So, these results could be explained not by a lack of reactivity of halo-oxybispyridines but by a lack of stability of the resulting boronic acids.

A range of efficient cross-coupling reactions of alkoxypyridyl boronic acids with selected aryl/heteroaryl halides have been described.[11] As illustrated in Scheme 6, the boronic acids **1**–**5** were efficiently coupled with aryl halides under standard Suzuki-type conditions,[12] furnishing a range of unknown pyridylethers **6**–**13** (Fig. 4) fully characterized and isolated.



Scheme 6. Suzuki cross-coupling of oxybispyridylboronic acids **1**–**5**.

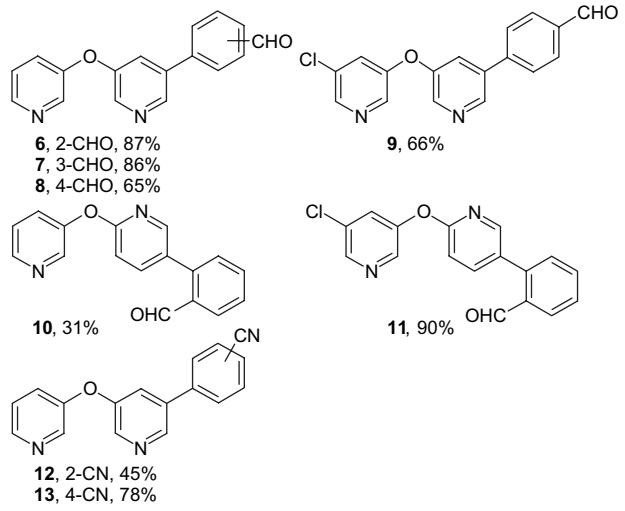


Figure 4. Pyridylethers **6**–**13**.

These pyridylethers were obtained with good yields except for compound **10**. This could be related to the relative instability of the corresponding boronic acid.

Pyridylethers **8**, **9** and **13**, which involve *p*-aryl halides, look like our model, RWJ-314313, so we have considered these compounds as potential ligands bound to the α4β2 nAChR subtype. Therefore, pharmacological studies are currently under investigation.

In conclusion, novel oxybispyridylboronic acids, which afford many potentialities particularly in metal-catalyzed cross-coupling reactions like Suzuki cross-coupling have been synthesized. Further experiments concerning the reactivity of these new compounds are currently under investigation. These new starting materials are used in the production of original libraries of oligopyridines. A detailed study of the Suzuki cross-coupling reaction will be published as soon as possible.

3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler heating bench and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX FT-IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants in Hertz. Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck) and spots were visualized using an ultraviolet-light lamp. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

Starting materials were purchased from Aldrich, Acros Organics and Alfa Aesar and used without purification.

3.2. General procedure 1 for the synthesis of oxybispyridylboronic acids 1–5

To a slurry of 2.5 M solution of *n*-BuLi (1.25 equiv) in anhydrous ether cooled to −78 °C was added dropwise a solution of halo-oxybispyridine (1 equiv) in anhydrous ether. The resulting mixture was allowed to react at this temperature for over 1.5 h. A solution of triisopropylborate (1.25 equiv) in anhydrous ether was then added dropwise, 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 1 M aqueous NaOH solution. The resulting aqueous layer was collected and acidified to pH 4 by dropwise addition of 6 N HCl, keeping the internal temperature below 5 °C. Extraction with ethyl acetate, evaporation of the organic layer

and crystallization from diethylether afford oxybispyridylboronic acids **1–5**.

3.2.1. 5-(Pyridin-3-yloxy)pyridin-3-yl boronic acid (1). 5-(Pyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a white solid (57%) using 3-bromo-5-(pyridin-3-yloxy)-pyridine according to general procedure 1. Mp 180 °C. IR (KBr): 3391, 1571, 1476, 1422, 1353, 1220, 1148, 1100, 1023, 947, 854, 706 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ=8.56 (s, 1H), 8.41–8.38 (m, 3H), 7.82–7.81 (m, 1H), 7.58–7.55 (m, 1H), 7.51–7.48 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ=154.4, 142.7, 142.5, 140.4, 139.3, 127.8, 127.1, 126.7, 103.3, C-3 not observed. Anal. Calcd for $C_{10}H_9BN_2O_3$: C, 55.61; H, 4.20; N, 12.97. Found: C, 55.28; H, 4.04; N, 12.59.

3.2.2. 5-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid (2). 5-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a yellow solid (35%) using 3-bromo-5-(5-chloropyridin-3-yloxy)pyridine according to general procedure 1. Mp 210 °C. IR (KBr): 3313, 1568, 1425, 1421, 1267, 1139, 1091, 956, 866, 720, 687 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ=8.58 (d, J=2.0, 1H), 8.42 (d, J=1.8, 1H), 8.40 (d, J=1.8, 1H), 8.37 (d, J=2.0, 1H), 7.86 (t, J=2.0, 1H), 7.59 (t, J=1.8, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ=151.6, 144.7, 142.5, 140.9, 140.1, 137.8, 127.1, 126.7, 103.9, C-3 not observed. Anal. Calcd for $C_{10}H_8BClN_2O_3$: C, 47.96; H, 3.22; N, 11.19. Found: C, 47.73; H, 3.09; N, 11.24.

3.2.3. 6-(Pyridin-3-yloxy)pyridin-3-yl boronic acid (3). 6-(Pyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a white solid (8%) using 3-bromo-6-(pyridin-3-yloxy)-pyridine according to general procedure 1 with 2.2 equiv of *n*-BuLi and 2.2 equiv of triisopropylborate. Mp 186 °C. IR (KBr): 3300, 1699, 1576, 1474, 1425, 1262, 1117, 1042, 887, 778 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.92 (d, J=2.4, 1H), 8.71 (dd, J=4.6, 1.4, 1H), 8.70 (s, 2H), 8.66 (d, J=2.4, 1H), 8.37 (dd, J=8.5, 2.4, 1H), 8.29 (part A of systAB, $^3J_{AB}$=8.3, J=2.4, 1.4, 1H), 7.98 (part B of systAB, $^3J_{AB}$=8.3, J=4.6, 1H), 7.32 (d, J=8.5, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=153.1, 150.1, 149.2, 146.1, 145.6, 143.3, 129.1, 124.4, 110.5, C-3 not observed. Anal. Calcd for $C_{10}H_9BN_2O_3$: C, 55.31; H, 4.20; N, 12.97. Found: C, 55.08; H, 4.06; N, 12.83.

3.2.4. 6-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid (4). 6-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a white solid (86%) using 3-bromo-6-(5-chloropyridin-3-yloxy)pyridine with 2.2 equiv of *n*-BuLi and 2.2 equiv of triisopropylborate. Mp 164 °C. IR (KBr): 3366, 3079, 1598, 1579, 1430, 1364, 1269, 1136, 1095, 938, 885, 660 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.51 (d, J=1.9, 1H), 8.45–8.44 (m, 2H), 8.28 (s, 2H), 8.19 (dd, J=8.3, 1.9, 1H), 7.93 (t, J=2.2, 1H), 7.12 (d, J=8.3, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=163.4, 153.1, 150.2, 146.0, 144.2, 141.8, 130.8, 129.3, 110.5, C-3 not observed. Anal. Calcd for $C_{10}H_8BClN_2O_3$: C, 47.96; H, 3.22; N, 11.19. Found: C, 47.71; H, 2.99; N, 10.84.

3.2.5. 6-(6-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid (5). 6-(6-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as an orange solid (20%) using 3-bromo-6-(6-chloropyridin-3-yloxy)pyridine with 2.2 equiv of *n*-BuLi and 2.2 equiv of triisopropylborate according to general procedure 1. Mp 192 °C. IR (KBr): 3360, 3079, 1598, 1576, 1430, 1389, 1364, 1269, 1226, 1101, 938, 885, 757 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.50 (d, J=1.9, 1H), 8.32 (d, J=2.4, 1H), 8.29 (s, 2H), 8.18 (d, J=8.2, 1H), 7.75 (dd, J=8.6, 2.4, 1H), 7.58 (d, J=8.6, 1H), 7.11 (d, J=8.2, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=163.5, 153.1, 149.5, 145.9, 145.3, 143.3, 133.2, 124.9, 110.6, C-3 not observed. Anal. Calcd for $C_{10}H_8BClN_2O_3$: C, 47.96; H, 3.22; N, 11.19. Found: C, 47.29; H, 3.19; N, 10.98.

3.3. General procedure 2 for the synthesis of pyridylethers 6–13

A mixture of oxybispyridylboronic acid (1.1 equiv), aryl halide (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 refluxed for 14 h (total consumption of aryl halide seen on TLC). Ethyl acetate and water were then added to the mixture. The organic layer was separated, dried over $MgSO_4$ and concentrated to dryness. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 80/20) to afford pyridylethers **6–13**.

3.3.1. 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (6). 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange solid (87%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 2-bromobenzaldehyde according to general procedure 2. Mp 88 °C. IR (KBr): 3042, 2762, 1686, 1591, 1572, 1474, 1436, 1416, 1305, 1227, 1194, 1019, 886, 800, 705, 643 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=9.93 (s, 1H), 8.51–8.47 (m, 3H), 8.40 (d, J=2.0, 1H), 7.96 (d, J=7.6, 1H), 7.77 (t, J=7.0, 1H), 7.68–7.59 (m, 3H), 7.54 (d, J=7.6, 1H), 7.46–7.43 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=191.6, 152.8, 152.2, 145.3, 145.1, 140.9, 140.4, 139.8, 134.9, 133.9, 133.5, 131.4, 128.9, 128.7, 127.1, 125.8, 124.8. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.69; H, 4.24; N, 10.25.

3.3.2. 3-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (7). 3-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange oil (86%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 3-bromobenzaldehyde according to general procedure 2. IR (KBr): 3055, 2730, 1698, 1578, 1475, 1423, 1377, 1303, 1238, 1188, 1022, 886, 800, 705, 649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H), 8.59 (m, 1H), 8.40–8.33 (m, 3H), 7.97 (d, J=1.2, 1H), 7.83 (dd, J=7.8, 1.2, 1H), 7.74 (dd, J=7.8, 1.2, 1H), 7.54 (t, J=7.8, 1H), 7.47–7.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.6, 153.2, 152.6, 145.3, 143.3, 141.3, 140.2, 137.5, 136.9, 136.4, 132.8, 131.3, 129.8, 128.4, 127.7, 125.7, 123.7. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.83; H, 4.02; N, 10.10.

3.3.3. 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (8). 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange solid (65%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 4-bromobenzaldehyde according to general procedure 2. Mp 80 °C. IR (KBr): 3051, 2733, 1702, 1604, 1567, 1474, 1443, 1423, 1298, 1229, 1184,

1019, 898, 803, 698, 647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H), 8.61 (d, J=2.3, 1H), 8.41 (d, J=2.3, 1H), 8.38–8.33 (m, 2H), 7.90 (part A of systAB, $^3J_{AB}$=8.3, 2H), 7.64 (part B of systAB, $^3J_{AB}$=8.3, 2H), 7.48 (t, J=2.3, 1H), 7.33 (part A of systAB, $^3J_{AB}$=8.3, J=2.7, 1.4, 1H), 7.27 (part B of systAB, $^3J_{AB}$=8.3, J=4.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.4, 153.2, 152.6, 145.4, 143.5, 142.4, 141.4, 140.6, 136.4, 134.5, 130.3 (2C), 127.7 (2C), 125.9, 124.3, 123.8. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.66; H, 4.35; N, 10.07.

3.3.4. 4-[5-(5-Chloropyridin-3-yloxy)pyridin-3-yl]benzaldehyde (9). 4-[5-(5-Chloropyridin-3-yloxy)pyridin-3-yl]-benzaldehyde was prepared as an orange solid (66%) using 5-(5-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **2** and 4-bromobenzaldehyde according to general procedure 2. Mp 110 °C. IR (KBr): 1694, 1606, 1572, 1440, 1421, 1296, 1246, 1219, 1094, 935, 823, 698, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H), 8.66 (d, J=1.8, 1H), 8.39 (d, J=1.8, 1H), 8.31 (d, J=2.4, 1H), 8.28 (d, J=2.4, 1H), 7.91 (part A of systAB, $^3J_{AB}$=8.1, 2H), 7.66 (part B of systAB, $^3J_{AB}$=8.1, 2H), 7.52 (t, J=1.8, 1H), 7.31 (t, J=2.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.3, 153.0, 152.4, 144.1, 143.9, 142.0, 140.8, 138.7, 136.6, 135.9, 131.9, 130.3 (2C), 127.7 (2C), 125.3, 124.5. Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; N, 9.01. Found: C, 65.56; H, 3.35; N, 8.92.

3.3.5. 2-[6-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (10). 2-[6-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange solid (31%) using 6-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **3** and 2-bromobenzaldehyde according to general procedure 2. Mp 82 °C. IR (KBr): 1692, 1591, 1571, 1447, 1426, 1418, 1306, 1221, 1154, 1029, 926, 849, 725, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.94 (s, 1H), 8.50 (d, J=2.4, 1H), 8.42 (d, J=4.6, 1H), 8.08 (d, J=2.7, 1H), 7.97 (dd, J=8.3, 2.4, 1H), 7.70 (dd, J=8.3, 2.7, 1H), 7.67 (part A of systAB, $^3J_{AB}$=7.5, J=7.8, 1.5, 1H), 7.54 (part A of systAB, $^3J_{AB}$=8.3, J=2.7, 1.2, 1H), 7.47–7.50 (m, 2H), 7.35 (dd, J=7.8, 2.1, 1H), 7.05 (d, J=8.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.3, 162.8, 150.3, 147.6, 145.2, 143.6, 141.1, 138.2, 134.3, 133.8, 131.0, 129.3, 129.0, 128.8, 128.6, 124.1, 111.3. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.73; H, 4.10; N, 10.07.

3.3.6. 2-[6-(5-Chloropyridin-3-yloxy)pyridin-3-yl]benzaldehyde (11). 2-[6-(5-Chloropyridin-3-yloxy)pyridin-3-yl]-benzaldehyde was prepared as a yellow solid (90%) using 6-(5-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **4** and 2-bromobenzaldehyde according to general procedure 2. Mp 130 °C. IR (KBr): 1695, 1599, 1573, 1469, 1427, 1304, 1272, 1249, 1020, 921, 848, 762, 685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=10.02 (s, 1H), 8.47 (d, J=2.2, 1H), 8.46 (d, J=2.2, 1H), 8.18 (d, J=2.2, 1H), 8.06 (dd, J=7.8, 2.2, 1H), 7.79 (dd, J=7.8, 1.9, 1H), 7.66 (t, J=2.2, 1H), 7.62 (part B of systAB, $^3J_{AB}$=7.3, J=7.8, 1.0, 1H), 7.64 (part A of systAB, $^3J_{AB}$=7.3, J=7.9, 1.9, 1H), 7.41 (dd, J=7.9, 1.0, 1H), 7.14 (d, J=7.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.2, 162.1, 147.4, 144.8, 144.6, 141.4, 141.3, 140.8, 138.4, 134.0, 133.7, 131.8, 129.8, 129.1, 128.9, 128.6, 111.4. Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; N, 9.01. Found: C, 65.49; H, 3.35; N, 8.89.

3.3.7. 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile (12). 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile was prepared as a white solid (45%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 2-bromobenzonitrile according to general procedure 2. Mp 124 °C. IR (KBr): 3026, 2218, 1591, 1574, 1476, 1416, 1229, 1096, 1021, 893, 790, 703 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.69 (s, 1H), 8.64 (d, J=1.9, 1H), 8.58 (d, J=1.9, 1H), 8.50 (d, J=4.4, 1H), 8.06 (d, J=7.8, 1H), 7.91–7.87 (m, 2H), 7.79 (d, J=7.8, 1H), 7.73–7.66 (m, 2H), 7.55–7.51 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=152.5, 152.4, 145.4, 144.5, 141.1, 140.1, 139.2, 134.7, 133.8, 133.7, 130.4, 129.2, 126.0, 125.9, 124.8, 118.1, 110.7. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.66; H, 4.09; N, 15.13.

3.3.8. 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile (13). 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile was prepared as an orange solid (78%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 4-bromobenzonitrile according to general procedure 2. Mp 128 °C. IR (KBr): 3052, 2222, 1604, 1569, 1473, 1425, 1217, 1105, 1016, 893, 802, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.51 (d, J=1.7, 1H), 8.34–8.29 (m, 3H), 7.62 (part A of systAB, $^3J_{AB}$=6.6, J=1.7, 1.7, 2H), 7.53 (part B of systAB, $^3J_{AB}$=6.6, J=1.7, 1.7, 2H), 7.48 (d, J=1.7, 1H), 7.28 (part A of systAB, $^3J_{AB}$=8.4, J=2.7, 1.4, 1H), 7.22 (part B of systAB, $^3J_{AB}$=8.4, J=4.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.2, 152.5, 145.3, 143.1, 141.2, 140.9, 140.6, 135.8, 132.7 (2C), 127.7 (2C), 125.9, 124.3, 123.6, 118.1, 112.1. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.18. Found: C, 74.55; H, 3.99; N, 14.89.

Acknowledgements

The authors thank Laboratoires Servier, Conseil Régional de Basse-Normandie and FEDER (Fonds Européens de Développement Economique Régional) for their financial support.

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