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Synthesis of novel halo-oxybispyridines, new building blocks in cholinergic medicinal chemistry

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Abstract—This paper describes a method for the preparation of oxybispyridines bearing several halogens, which could be further transformed into other functional groups thus giving access to libraries with the bis-pyridyl ether moiety as the common structural feature of interest in cholinergic medicinal chemistry. Scope and limitation of the method are outlined.

1. Introduction

A considerable amount of literature has been published concerning the pyridylethers as nicotinic cholinergic receptor ligands. For example, A-85380 and its derivatives,[1] ABT-594[2] and ABT-089[3] have been described to be highly selective agents of $\alpha_4\beta_2$ receptors (Fig. 1).

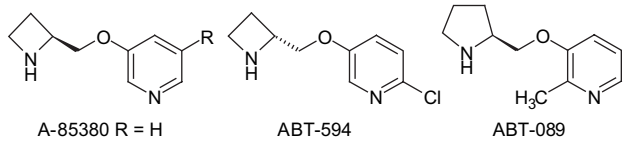

Figure 1. Pyridylethers as nicotinic cholinergic agonists ($\alpha_4\beta_2$).

Besides, synthesis and structure–activity relationship of novel pyridylethers have been published by Lee et al.[4] The authors described that the only criteria left on the molecule was to place the second nitrogen in an optimal distance from the 3-position of the pyridine.

From these observations, numerous derivatives have been synthesized and among them, RWJ-314313[4] as a potent ligand bound to the $\alpha_4\beta_2$ nAChR subtype (Fig. 2).

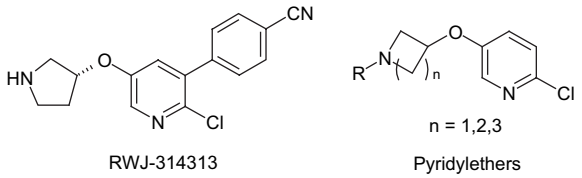

Figure 2.

In this study, we chose to develop the synthesis of novel pyridylethers such as halo-oxybispyridines. A few examples of symmetrical and dissymmetrical oxybispyridines have been described[5–8] and some of these were obtained through nucleophilic substitution.[9–12]

Indeed, from a synthetic point of view, halo-oxybispyridines afford more potentialities because of particular reactivity in metal-catalyzed cross-coupling reactions like Suzuki coupling, either as electrophilic agents or in preparing their own boronic acids. In this study, we pay particular attention to synthesize various halo-oxybispyridines as valuable building blocks.

The two methodologies allowing the preparation of oxybispyridines (Scheme 1) are as follows: either the Chan–Lam coupling reaction[13–15] or the nucleophilic substitution. For these two reactions, halohydroxypyridines have to be prepared. Recently, we described a general method for the synthesis of halohydroxypyridines from novel halopyridylboronic acids and esters using an efficient hydroxydeboronation reaction.[17]

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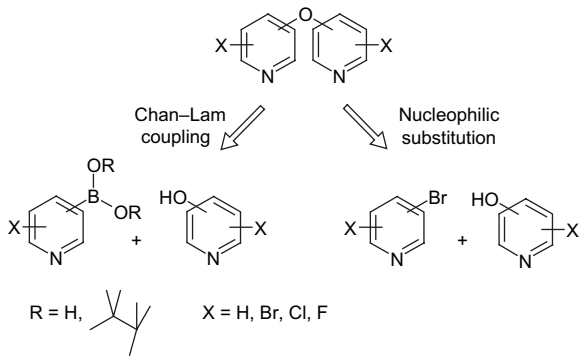


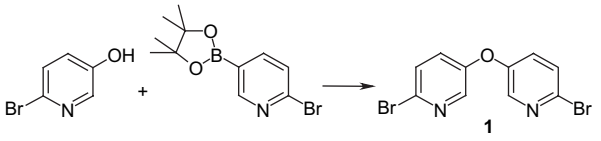
Scheme 1. Two synthetic approaches to halo-oxybispyridines.

2. Results and discussion

The Chan–Lam coupling reaction has been considered first because of our knowledge in the halopyridylboronic acid synthesis[18–21] and in the study of their reactivity in cross-coupling reactions illustrated, for example, by the synthesis of the quaterpyridine nemertelline[22] and in the Petasis reaction.[23]

Firstly, halopyridylboronic acids have been used under classical conditions,[13–14] but the reaction was unsuccessful. Secondly, halopyridylboronic esters have been involved, considering our precedent and fruitful works concerning N-arylations.[24] Several conditions were then tested at room temperature (if no reaction occurred, the mixture was then heated to reflux). All these tests are summarized in Table 1.

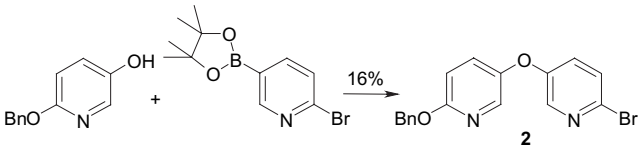
Table 1. Several conditions for Chan–Lam coupling reaction (NR: no reaction)



Entry	$Cu(OAc)_2$	Base	Solvent	Yields
1[13,14]	1 equiv	Pyridine	CH_2Cl_2	11%
2[13,14]	1 equiv	Pyridine	DMF	NR
3[13,14]	1 equiv	$N(Et)_3$	CH_2Cl_2	NR
4[13,14]	1 equiv	$N(Et)_3$	DMF	NR
5	1.5 equiv	Pyridine	CH_2Cl_2	NR
6	1.5 equiv	$N(Et)_3$	CH_2Cl_2	NR
7[16]	Cat., 5% TEMPO/air	Pyridine	CH_2Cl_2	NR
8[16]	Cat., 5% TEMPO/air	$N(Et)_3$	CH_2Cl_2	NR

The coupling reaction of 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 6-bromo-pyridin-3-ol gave the expected dibromo-oxybispyridine **1** when the reaction was carried out as follows: 1 equiv of copper(II) acetate, 5 equiv of pyridine in dichloromethane, and 4 Å molecular sieves at room temperature for 4 days (entry 1). Other procedures (entry 2–8) gave either trace of the expected product or degradation products.

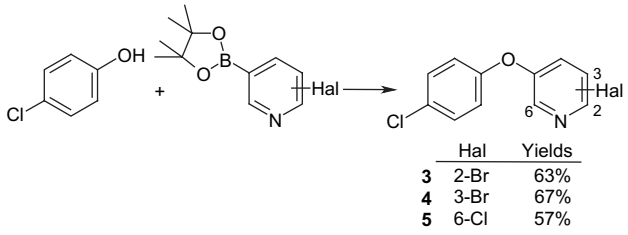
According to these conditions, the reaction of 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 2-benzyloxy-5-(6-bromopyridin-3-yloxy)pyridine gave the expected product **2** (Scheme 2).



Scheme 2. Synthesis of oxybispyridine **2**. Reagents and conditions: $Cu(Ac)_2$ (1 equiv), pyridine (5 equiv), CH_2Cl_2, 4 Å molecular sieves, 25 °C, 4 days.

But, this route to obtain novel halo-oxybispyridines led to poor results even if two examples **1** and **2** have been produced with 11 and 16% yields, respectively.

To explain this lack of reactivity, we suggested that when the hydroxyl compound used in coupling reactions contained an electron-withdrawing group, the reaction was unsuccessful. More precisely, the coordination step seemed to depend on the stability of the anion in accordance with the pK_a of the hydroxyl compound. Indeed, we considered the coupling reaction of *p*-chlorophenol and halopyridylboronic esters in the previous conditions. We obtained arylheteroarylethers **3–5** with 63, 67, and 57% yields, respectively (Scheme 3).



Scheme 3. Synthesis of arylheteroarylethers **3–5**. Reagents and conditions: $Cu(Ac)_2$ (1 equiv), pyridine (5 equiv), CH_2Cl_2, 4 Å molecular sieves, 25 °C, 4 days.

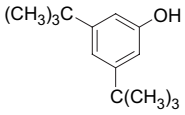
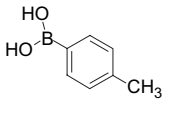
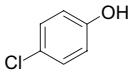
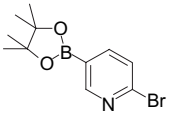
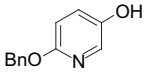
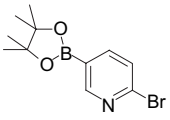
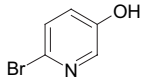
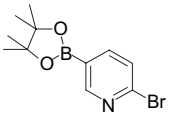
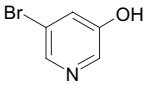
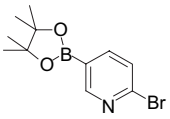
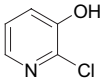
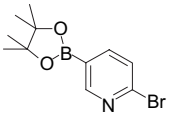
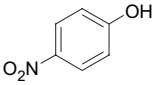
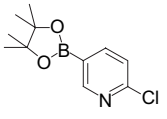
We observed the same trend with several hydroxyl compounds, shown in Table 2: the higher the pK_a value is, the more unstable the anion is and the more efficient the coordination step is.

These results confirmed the lack of reactivity of halohydroxypyridines in Chan–Lam coupling reaction, which did not seem to be good supports because of the electron deficient feature of pyridine derivatives.

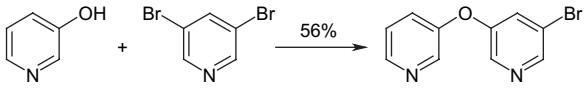
A second strategy has been considered to synthesize halo-oxybispyridines. Recently, Dull et al.[12] have described the synthesis of aryl olefinic azacyclic and aryl acetylenic azacyclic compounds, which is able to affect the nicotinic cholinergic receptors and to be agents for the treatment of central nervous system disorders. Among these compounds, only one halo-oxybispyridine has been described in this patent, 3-bromo-5-(pyridin-3-yloxy)-pyridine. This compound was obtained by nucleophilic substitution from pyridin-3-ol and 3,5-dibromopyridine (Scheme 4).

So, we took into account this strategy and we optimized this reaction in order to make it applicable not only to various 3,3′-oxybispyridines, but also to 2,3′- and 4,4′-oxybispyridines (Scheme 5).

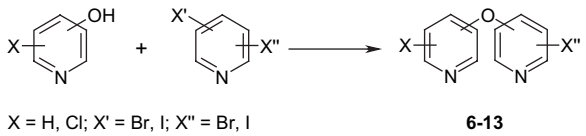
Table 2. Influence of the pK_a value in Chan–Lam coupling reaction[a]

Entry	Hydroxyl components (pK_a^*)	Boronic components	Yields
1[14b]	 (9.63)		79%
2	 (9.26)		63%
3	 (9.17)		16%
4	 (8.53)		11%
5	 (8.32)		NR
6	 (7.78)		NR
7	 (7.04)		NR

[a] Theoretical value.[25]



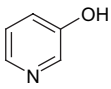
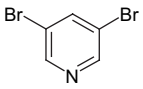
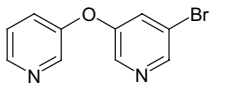
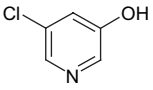
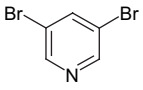
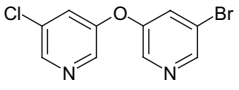
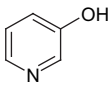
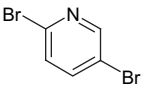
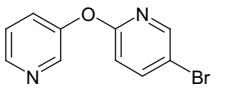
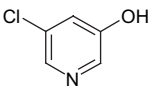
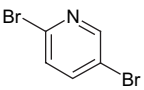
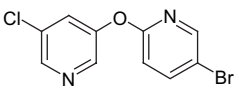
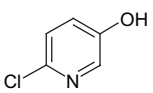
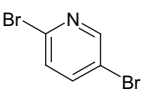
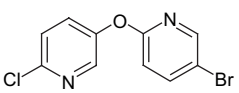
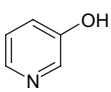
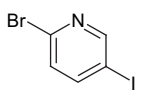
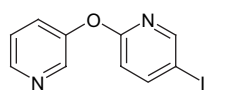
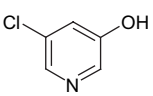
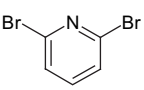
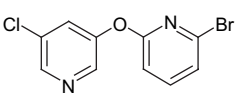
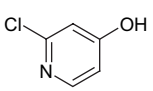
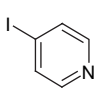
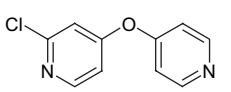
Scheme 4. Synthesis of halo-oxybispyridine. Reagents and conditions: NaH 80% (1 equiv), DMF, 130 °C, 20 h.



Scheme 5. Synthesis of halo-oxybispyridines **6–13**. Reagents and conditions: 60% NaH (1.25 equiv), DMF, reflux, 48 h.

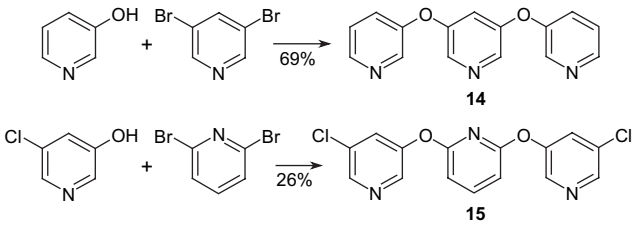
Fortunately, we have easily achieved numerous isomers and this methodology is now applicable to a large scale of starting materials. It has been used with several halohydroxypyridines and halopyridines to obtain novel halo-oxybispyridines **6–13** as shown in Table 3.

Table 3. Novel halo-oxybispyridines **6–13**

Entry	Halohydroxy-pyridines	Halopyridines	Halo-oxybispyridines	Yields
1			 **6**	66%
2			 **7**	31%
3			 **8**	66%
4			 **9**	72%
5			 **10**	63%
6			 **11**	23%
7			 **12**	27%
8			 **13**	63%

The nucleophilic substitution led to good yields whether in 2-position (entries 3, 4, and 5), in 3-position (entry 1) or in 4-position (entry 8) of the nitrogen of pyridine. But, according to the position and the nature of the halogen, yields have been reduced by half. Moreover, the residual halogen of halo-oxybispyridines can be involved in a second nucleophilic substitution. Therefore, the heterogeneity of yields can be warranted by formation of a small amount of secondary products as dioxyterpyridines. In order to clearly identify the structure of these secondary products, we have synthesized 3,5-di-(pyridin-3-yloxy)pyridine **14** by reaction of 3,5-dibromopyridine with pyridin-3-ol and 2,6-di-(5-chloropyridin-3-yloxy)pyridine **15** by reaction of 2,6-dibromopyridine with 5-chloropyridin-3-ol with 69 and 26% yields, respectively (Scheme 6). Those synthesized dioxyterpyridines matched to the by-products previously identified in the reaction.

It is to be noted that the nucleophilic substitution would have been better with chlorinated compounds, but halogen–metal exchange considered in further works is not possible with chlorinated halo-oxybispyridines.



Scheme 6. Synthesis of dioxybisterpyridines **14** and **15**. Reagents and conditions: 60% NaH (1.25 equiv), DMF, reflux, 48 h.

In conclusion, we have produced novel oxybispyridines bearing several halogens. Further experiments concerning the reactivity of these compounds are currently under investigation in order to use them as new building blocks in the production of pyridine compounds with potential cholinergic activity.

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 FTIR 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. 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 with an ultraviolet-light lamp. Elemental analyzes for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

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

Analytical data for known compounds were always fully consistent with published data.

3.2. General procedure 1 for the synthesis of arylheteroarylethers using Chan–Lam coupling reaction (1 and 5)

To a stirred solution of halopyridylboronic ester (2 equiv) and halopyridinol or halophenol (1 equiv) in dichloromethane was added copper(II) acetate (1 equiv), pyridine (5 equiv), and 4 Å molecular sieves. The reaction was then continued at room temperature for 4 days. The mixture was filtered, concentrated to dryness, and the residue was purified by column chromatography (cyclohexane/ethylacetate, 90/10) to afford ethers **1** and **5**.

3.2.1. 2-Bromo-5-(6-bromopyridin-3-yloxy)pyridine (1). 2-Bromo-5-(6-bromopyridin-3-yloxy)pyridine was prepared using 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 6-bromopyridin-3-ol according to general procedure 1 as a white solid (11%). Mp 82 °C. IR (KBr): 1680, 1573, 1349, 1329, 1271, 1179, 1069, 929, 754, 642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.86–7.85 (m, 2H), 7.44–7.43 (m, 2H), 7.27–7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2, 140.9, 138.8, 131.1, 122.0. Anal. Calcd for $C_{10}H_6Br_2N_2O$: C, 36.40; H, 1.83; N, 8.49. Found: C, 36.09; H, 1.54; N, 7.98.

3.2.2. 2-Benzyloxy-5-(6-bromopyridin-3-yloxy)pyridine (2). 2-Benzyloxy-5-(6-bromopyridin-3-yloxy)pyridine was prepared using 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 6-benzyloxypyridin-3-ol according to general procedure 1 as a white solid (16%). Mp 74 °C. IR (KBr): 1678, 1575, 1420, 1345, 1360, 1276, 1186, 1091, 938, 742, 718, 653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.06 (d, J=2.9 Hz, 1H), 7.91 (d, J=2.8 Hz, 1H), 7.40–7.24 (m, 7H), 7.06 (dd, J=8.7, 3.0 Hz, 1H), 6.77 (d, J=8.9 Hz, 1H), 5.29 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.9, 153.5, 152.9, 141.0, 138.9, 137.6, 136.9, 131.5, 129.8 (2C), 128.3 (2C), 127.4, 126.5, 125.2, 115.5, 69.4. Anal. Calcd for $C_{17}H_{13}BrN_2O_2$: C, 57.16; H, 3.67; N, 7.84. Found: C, 56.68; H, 3.40; N, 7.54.

3.2.3. 2-Bromo-5-(4-chlorophenoxy)pyridine (3). 2-Bromo-5-(4-chlorophenoxy)pyridine was prepared using 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxa-borolane and *p*-chlorophenol according to general procedure 1 as a white solid (63%). Mp 68 °C. IR (KBr): 1486, 1449, 1375, 1262, 1088, 1009, 828 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.23 (d, J=4.6 Hz, 1H), 7.64 (d, J=8.3 Hz, 1H), 7.48–7.44 (m, 3H), 7.13 (d, J=8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.5, 153.4, 141.2, 135.0, 130.2 (2C), 129.8, 128.7, 128.4, 120.3 (2C). Anal. Calcd for $C_{11}H_7BrClNO$: C, 46.43; H, 2.48; N, 4.92. Found: C, 46.12; H, 2.71; N, 4.71.

3.2.4. 3-Bromo-5-(4-chlorophenoxy)pyridine (4).[26] 3-Bromo-5-(4-chlorophenoxy)pyridine was prepared using 2-[3-(5-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and *p*-chlorophenol according to general procedure 1 as an orange solid (67%). Mp 79 °C. IR (KBr): 1554, 1484, 1425, 1307, 1250, 1200, 1087, 1009, 894, 871, 844 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.35 (s, 1H), 8.24 (s, 1H), 7.35 (s, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.77 (d, J=8.8 Hz, 2H).

3.2.5. 2-Chloro-3-(4-chlorophenoxy)pyridine (5).[27] 2-Chloro-3-(4-chlorophenoxy)pyridine was prepared using 2-[3-(2-chloro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and *p*-chlorophenol according to general procedure 1 as a white solid (57%). Mp<50 °C. IR (KBr): 1498, 1454, 1367, 1262, 1087, 1011, 824 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.26 (d, J=4.6 Hz, 1H), 7.59 (d, J=8.1 Hz, 1H), 7.48–7.44 (m, 3H), 7.06 (d, J=8.9 Hz, 2H).

3.3. General procedure 2 for the synthesis of halo-oxybispyridines using nucleophilic substitution (6 and 13)

To a stirred solution of pyridin-3-ol or chloropyridinol (1 equiv) in dimethylformamide was slowly added 60% sodium hydride (1.25 equiv). The mixture was then continued at room temperature for 1 h and mono- or di-halopyridine (0.55 equiv) was added. The mixture was refluxed for 48 h and then was allowed to warm to room temperature. To the resulting suspension was added water. The mixture was then extracted with ether and the extract was washed with

brine, dried over magnesium sulfate, and concentrated on rotary evaporator. The residue was purified by column chromatography (cyclohexane/ethylacetate, 80/20) to afford halo-oxybispyridines **6** and **13**.

3.3.1. 3-Bromo-5-(pyridin-3-yloxy)pyridine (6).[12] 3-Bromo-5-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol and 3,5-dibromopyridine according to general procedure 2 as an orange oil (66%). IR (KBr): 1565, 1475, 1423, 1305, 1258, 1086, 1021, 902, 798, 708, 673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.22 (d, J=2.4 Hz, 1H), 8.20–8.19 (m, 2H), 8.36 (d, J=2.7 Hz, 1H), 7.48 (t, J=2.4 Hz, 1H), 7.15 (part A of system AB, $^3J_{AB}$=8.6 Hz, J=2.7, 1.7 Hz, 1H), 7.10 (part B of system AB, $^3J_{AB}$=8.6 Hz, J=4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.7, 152.1, 145.6, 145.5, 141.2, 139.4, 128.3, 126.3, 124.8, 120.1.

3.3.2. 3-Bromo-5-(5-chloropyridin-3-yloxy)pyridine (7). 3-Bromo-5-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol and 3,5-dibromopyridine according to general procedure 2 as a white solid (31%). Mp 72 °C. IR (KBr): 1555, 1412, 1310, 1251, 1092, 1015, 925, 899, 866, 692, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.54 (d, J=2.2 Hz, 1H), 8.43 (d, J=2.2 Hz, 1H), 8.38 (d, J=2.2 Hz, 1H), 8.33 (d, J=2.2 Hz, 1H), 7.52 (t, J=2.2 Hz, 1H), 7.37 (t, J=2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.7, 152.6, 146.8, 144.7, 139.7, 139.1, 132.5, 128.7, 125.9, 120.7. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 41.91; H, 1.98; N, 9.69.

3.3.3. 3-Bromo-6-(pyridin-3-yloxy)pyridine (8). 3-Bromo-6-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol and 2,5-dibromopyridine according to general procedure 2 as a beige solid (66%). Mp<50 °C. IR (KBr): 1575, 1455, 1367, 1268, 1091, 1004, 881, 707, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.41 (d, J=2.4 Hz, 1H), 8.36 (dd, J=4.6, 1.4 Hz, 1H), 8.07 (d, J=2.4 Hz, 1H), 7.69 (dd, J=8.6, 2.4 Hz, 1H), 7.40 (part A of system AB, $^3J_{AB}$=8.3 Hz, J=2.4, 1.4 Hz, 1H), 7.22 (part B of system AB, $^3J_{AB}$=8.3 Hz, J=4.6 Hz, 1H), 6.81 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.3, 149.9, 147.7, 145.6, 143.2, 141.9, 128.3, 123.6, 113.9, 112.9. Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.37; H, 2.88; N, 11.42.

3.3.4. 3-Bromo-6-(5-chloropyridin-3-yloxy)pyridine (9). 3-Bromo-6-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol and 2,5-dibromopyridine according to general procedure 2 as a white solid (72%). Mp 80 °C. IR (KBr): 1574, 1458, 1366, 1272, 1094, 1022, 921, 888, 826, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.42 (d, J=1.9 Hz, 1H), 8.39 (d, J=2.4 Hz, 1H), 8.19 (d, J=2.7 Hz, 1H), 7.84 (dd, J=8.7, 2.7 Hz, 1H), 7.57 (t, J=1.9, 2.4 Hz, 1H), 6.94 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.1, 150.1, 147.6, 144.5, 142.9, 141.7, 130.8, 129.2, 114.3, 113.8. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 41.73; H, 2.02; N, 9.47.

3.3.5. 3-Bromo-6-(6-chloropyridin-3-yloxy)pyridine (10). 3-Bromo-6-(6-chloropyridin-3-yloxy)pyridine was prepared using 6-chloropyridin-3-ol and 2,5-dibromopyridine according to general procedure 2 as a white solid (63%). Mp 80 °C. IR (KBr): 1574, 1458, 1427, 1415, 1366, 1273, 1130, 1094, 1022, 922, 888, 826, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=2.8 Hz, 1H), 8.08 (d, J=2.8 Hz, 1H), 8.19 (dd, J=8.7, 2.8 Hz, 1H), 7.42 (dd, J=8.6, 2.8 Hz, 1H), 7.27 (d, J=8.6 Hz, 1H), 6.85 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.2, 149.2, 147.9, 146.6, 143.0, 142.4, 131.8, 124.6, 114.5, 113.3. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 42.19; H, 2.05; N, 9.22.

3.3.6. 3-Iodo-6-(pyridin-3-yloxy)pyridine (11). 3-Iodo-6-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol and 2-bromo-5-iodopyridine according to general procedure 2 as a yellow oil (23%). IR (KBr): 1573, 1469, 1367, 1269, 1102, 1014, 891, 798, 715, 656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.39 (d, J=2.4 Hz, 1H), 8.36 (dd, J=4.6, 1.4 Hz, 1H), 8.21 (d, J=2.2 Hz, 1H), 7.83 (dd, J=8.6, 2.2 Hz, 1H), 7.39 (part A of system AB, $^3J_{AB}$=8.3 Hz, J=2.4, 1.4 Hz, 1H), 7.22 (part B of system AB, $^3J_{AB}$=8.3 Hz, J=4.6 Hz, 1H), 6.71 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 152.9, 149.9, 147.4, 145.7, 143.2, 128.4, 123.7, 113.7, 84.8. Anal. Calcd for $C_{10}H_7IN_2O$: C, 40.29; H, 2.37; N, 9.40. Found: C, 40.12; H, 2.16; N, 9.18.

3.3.7. 2-Bromo-6-(5-chloropyridin-3-yloxy)pyridine (12). 2-Bromo-6-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol and 2,6-dibromopyridine according to general procedure 2 as a beige oil (27%). IR (KBr): 1609, 1579, 1558, 1509, 1418, 1304, 1242, 1186, 1160, 1090, 1015, 927, 869, 775, 723, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.36 (d, J=2.4 Hz, 1H), 8.29 (d, J=2.0 Hz, 1H), 7.53 (t, J=2.0, 2.4 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 6.13 (d, J=8.0 Hz, 1H), 6.08 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.8, 156.0, 151.0, 143.5, 141.6, 140.7, 131.2, 128.5, 100.4, 96.8. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 42.54; H, 2.02; N, 9.37.

3.3.8. 2-Chloro-4-(pyridin-4-yloxy)pyridine (13). 2-Chloro-4-(pyridin-4-yloxy)pyridine was prepared using 2-chloropyridin-4-ol and 4-iodopyridine according to general procedure 2 as a beige solid (63%). Mp 75 °C. IR (KBr): 1571, 1430, 1429, 1373, 1257, 1098, 1021, 1009, 929, 890, 823, 653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.73 (d, J=5.5 Hz, 2H), 8.12 (d, J=5.5 Hz, 1H), 6.79 (d, J=5.5 Hz, 2H), 6.70 (dd, J=5.5, 2.7 Hz, 1H), 6.65 (d, J=2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 162.8, 153.2, 152.1 (2C), 150.8, 116.3, 114.8 (2C), 111.4. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56. Found: C, 58.07; H, 3.34; N, 13.45.

3.4. General procedure 2 for the synthesis of dioxyterpyridines using nucleophilic substitution (14 and 15)

3.4.1. 3,5-Di-(pyridin-3-yloxy)pyridine (14). 3,5-Di-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol (2 equiv) and 3,5-dibromopyridine (0.55 equiv) according to general procedure 2 as a brown oil (69%). IR (KBr): 3044, 1565, 1475, 1424, 1305, 1253, 1209, 1021, 903, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.37–8.36 (m, 6H), 8.24 (t, J=2.2 Hz, 1H), 7.30–7.23 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.6, 152.6, 149.5, 135.0, 134.8,

126.7, 122.3, 111.5. Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.23; H, 4.08; N, 15.86.

3.4.2. 2,6-Di-(5-chloropyridin-3-yloxy)pyridine (15). 2,6-Di-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol (2 equiv) and 2,6-dibromopyridine (0.55 equiv) according to general procedure 2 as a yellow solid (26%). Mp 62 °C. IR (KBr): 1572, 1469, 1427, 1418, 1287, 1243, 1189, 1021, 912, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=1.9 Hz, 2H), 8.10 (d, J=2.0 Hz, 2H), 7.61 (t, J=7.8 Hz, 1H), 7.24 (t, J=2.0 Hz, 2H), 7.24 (t, J=7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.6, 154.3, 150.9, 144.8, 134.8, 132.4, 120.4, 111.3. Anal. Calcd for $C_{15}H_9Cl_2N_3O_2$: C, 53.92; H, 2.71; N, 12.57. Found: C, 53.65; H, 2.11; N, 12.13.

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