Novel 2,4,5-Trisubstituted Pyridines as Key Intermediates for the Preparation of the TSPO Ligand 6-F-PBR28: Synthesis and Full ^{1}H and ^{13}C NMR Characterization

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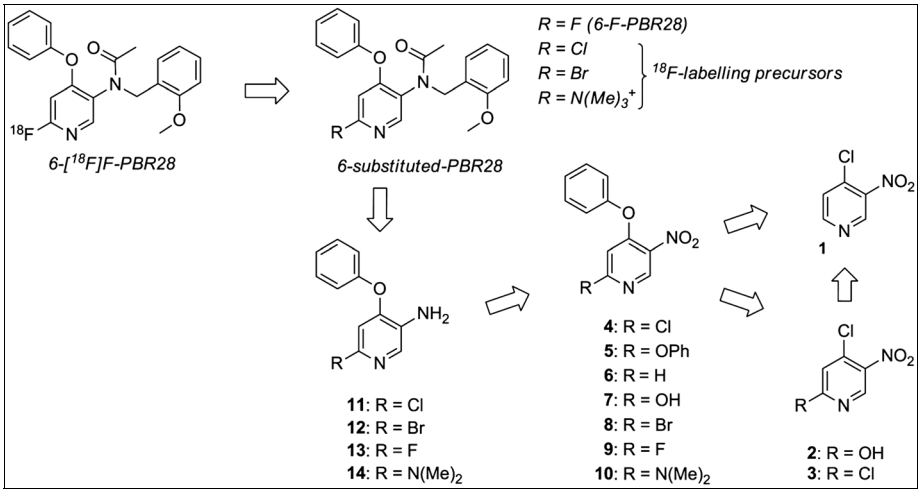
Received February 9, 2012
DOI 10.1002/jhet.1723
Published online 18 November 2013 in Wiley Online Library (wileyonlinelibrary.com).



As part of our ongoing research for molecular structures binding to the translocator protein (TSPO 18 kDa), we investigated the preparation of a number of new 2,4,5-trisubstituted pyridines as novel building blocks. In particular, 5-amino-2-halo-4-phenoxypyridines (**11–13**) were designed as key intermediates for the synthesis of the recently developed TSPO ligand 6-F-PBR28 and its fluorine-18-labeled version for positron emission tomography, 6-[^{18}F]F-PBR28. We hereby report the chemical preparation as well as the ^{1}H and ^{13}C NMR spectroscopic data of polysubstituted pyridines **2–14**. The latter demonstrates dramatic changes in electron density repartition of the aromatic ring upon substitution.

J. Hetercyclic Chem., **51**, 404 (2014).

INTRODUCTION

For many years, our laboratory has been interested in the preparation and use of positron-emitting radiolabeled probes (or radiotracers) for *in vivo* imaging using the powerful positron emission tomography tool [1]. In the positron emission tomography community, there has recently been a strong interest for the discovery of new radioligands targeting the translocator protein (TSPO 18 kDa) [2,3], formerly known as the peripheral benzodiazepine receptor (PBR), as radiomarkers of neuroinflammation and potential useful probes for early detection of neurodegenerative disorders and, in particular, radioligands labeled with the short-lived positron emitter fluorine-18 (half-life = 109.8 min). PBR-28 [4], a compound belonging to one of the most promising TSPO radiotracer families, has attracted much of our attention because it features a pyridine motif that is of particular interest when designing novel radiofluorinated probes. Indeed, this small heterocycle opens up the option of a fluorine-18 introduction at an α-position to the ring nitrogen using the well-established nucleophilic *ortho–hetero*aromatic radiofluorination methodology [5]. Besides being rapid (a few minutes) and often reported to proceed with high yields (>70%), these reactions lead to a positioning of the radioactive atom in the probe that is relatively stable metabolically (C(sp^2)-F bond), a considerable advantage when compared with the traditionally dominating aliphatic nucleophilic radiofluorination methodology (C(sp^3)-F bond formation) [6–8]. For these reasons, we have a long-standing interest in molecules bearing a 2-fluoropyridine moiety, and we have already reported several 2-[^{18}F] fluoropyridinyl-containing structures, for use either as radioligands [9–16] or as reagents dedicated to the radiolabeling of more complex structures such as oligonucleotides, peptides, or proteins [17–20] by prosthetic conjugation approaches.

The development of such fluorine-18-labeled compounds constructed around a pyridine core usually requires the prior synthesis of their α-halo-, α-nitro-, or α-trimethylammonium-counterparts as labeling precursors for aromatic nucleophilic radiofluorination as well as the α-fluoro—fluorine-19 (stable)—derivative as standard reference. The present paper aims at detailing the synthesis as well as the ^{1}H and ^{13}C NMR signal assignments of some new 2,4,5-trisubstituted pyridines that have been recently prepared in our laboratory

as scaffolds for the preparation of the recently developed TSPO 18 kDa radioligand 6-[^{18}F]F-PBR28 [16]. Most of them are halogenated pyridines and might also be useful building blocks for the design of more complex heteroaromatic compounds by means of cross-coupling reactions for instance.

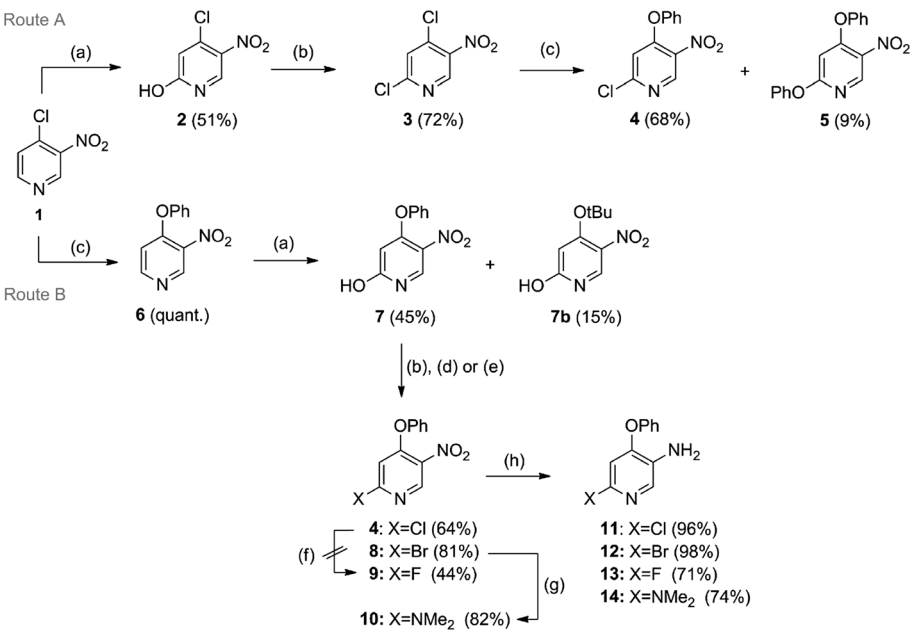
Throughout this paper, α, β, and γ designate the positions relative to the ring nitrogen.

RESULTS AND DISCUSSION

We started with the preparation of 2-chloro-5-nitro-4-phenoxypyridine **4** (Scheme 1) as key intermediate. Two synthetic routes were explored for the generation of this compound. In the first route (route A), hydroxylation at the C6 position of the commercially available 4-chloro-3-nitropyridine (**1**) was performed prior to the displacement of the 4-chlorine by the phenolate anion. Thus, selective hydroxylation of 4-chloro-3-nitropyridine (**1**) at the position *para* to the nitro group was performed in DMF using *tert*-butyl hydroperoxide (*t*-BuOOH) in the presence of potassium *tert*-butoxide (*t*-BuOK) as a base [21,22] to afford 4-chloro-5-nitropyridin-2-ol (**2**) in 51% yield. This intermediate was then treated with phosphorus oxychloride in refluxing toluene to provide 2,4-dichloro-5-nitropyridine (**3**) in good yield (72%). The 4-chlorine was then displaced, with preference over the 2-chlorine, by the phenolate anion generated with phenol and NaH in THF. Indeed, leaving groups at 4-position relative to the pyridine ring nitrogen are usually more reactive than those at 2-position [23]. The general order of reactivity of each position of pyridine halides, C4>C2>>C3, has been observed for many S_NAr displacements. In our particular case, 4-position is even more reactive because the nitro group diminishes also inductively the electron density at the vicinal C4 position. Thus, selective displacement of 4-Cl with phenolate anion was successfully achieved, and compound **4** was exclusively obtained (68%) over its C2-regioisomer whose formation was not observed (Scheme 1, route A). Nevertheless, formation of a non-negligible amount of 2,4-diphenoxy-5-nitropyridine **5** (9%), whose polarity is very close to the one of the desired molecule, prompted us to find an alternative way, more adequate to the gram scale, of preparing compound **4**.

A more efficient route for the preparation of 2-chloro-5-nitro-4-phenoxypyridine (**4**) was then developed by carrying out the displacement of the 4-chlorine with the phenolate anion prior to the α-functionalization (2-hydroxy introduction) of the pyridine ring, avoiding the formation of undesired 2,4-diphenoxy-5-nitropyridine (**5**). Thus, treatment of 4-chloro-3-nitropyridine (**1**) with phenol and NaH in THF at room temperature gave quantitatively the 3-nitro-4-phenoxypyridine (**6**), which was selectively hydroxylated at the C6 position with *tert*-butyl hydroperoxide via vicarious nucleophilic substitution of hydrogen in presence of *t*-BuOK as a base. Despite the low

Scheme 1. Synthetic approaches for the preparation of various 2,4,5-trisubstituted pyridines.



Reagents and conditions: (a) *t*-BuOOH, *t*-BuOK, DMF, -35°C, 2 h; (b) $POCl_3$, toluene, 110°C, 6 h; (c) NaH, PhOH, THF, rt, overnight; (d) $POBr_3$, toluene, 110°C, 2 h; (e) DAST, CH_3CN, 75°C, 6 h; (f) KF, DMF, 90°C; (g) *Method A:* $NHMe_2$, *t*-BuOK, dppp, $Pd(OAc)_2$, 70°C (10 to 46% yield) or *Method B*: $NHMe_2$.HCl, DMF, 120°C, 16 h (82% yield); (h) Fe, AcOH, 90°C, 30 min.

nucleophilicity of *t*-BuOK and the low reaction temperature (−50 to −30°C), compound **7** was obtained in only moderate yield (38–45%) because of side-products formation. In particular, displacement of the very labile C4 phenoxy group, because of activation by both the ring nitrogen atom and the *ortho* nitro group, was concomitantly observed resulting in the formation of undesired 5-nitro-4-*tert*-butoxypyridin-2-ol (**7b**) (15%) that was easily isolated from the crude because of its poor solubility in dichloromethane. Hydroxypyridine **7** was then converted to the corresponding 2-chloro-5-nitro-4-phenoxypyridine (**4**) in 64% yield with $POCl_3$ in refluxing toluene. 2-bromo-5-nitro-4-phenoxy-pyridine (**8**) was exclusively prepared following the second strategy (route B, Scheme 1) using $POBr_3$ as brominating agent in the third step (81% yield) of the synthetic sequence.

The preparation of the 2-fluoro-counterpart (**9**) of compounds **4** and **8** was first attempted from the chloro-analog **4** using the well-known potassium fluoride (KF) exchange technique [24]. Thus, 2-chloro-5-nitro-4-phenoxypyridine (**4**) was treated with KF in DMF at 90°C, and the reaction was monitored by TLC. Unfortunately, fluorination of **4** failed to provide any expected product, and all efforts (temperature, solvent, or fluorine salt changes) to introduce the fluorine atom by substituting the chlorine were unsuccessful. Possibly, the phenoxy group was the first displaced because of the predominant attractive effect of the *ortho*–nitro substituent on 4-position [23]. Therefore, an alternative strategy was considered to obtain compound **9**. We observed that the 2-hydroxy group of pyridinol **7** could be successfully replaced with fluorine when reacted with DAST (*N*,*N*-diethylaminosulfur trifluoride) in acetonitrile at 75°C (44% yield). Direct fluorination of hydroxyl group on an activated heteroaromatic ring using DAST or a similar deoxo-fluorinating agent has not been reported in the literature [16].

Introduction of a dimethylamino group at the 2-position of the pyridine ring was envisaged via displacement of the 2-bromine atom in compound **8**. Considering that the 2-position and 4-position in pyridine **8** are both highly activated [25] because of the presence of the ring nitrogen (α and γ activation) and the nitro group (*ortho* and *para* activation) with a higher inductive effect at the 4-position (Scheme 2), a palladium-catalyzed carbon–nitrogen bond formation, commonly known as the Buchwald–Hartwig amination reaction [26,27], was envisaged for the introduction of a dimethylamino group regioselectively at the 2-position. The reaction was carried out as described by Wagaw *et al* [28] for the synthesis of aminopyridines. Substituted 2-bromopyridine **8** was reacted with dimethylamine and *t*-BuOK in the presence of palladium acetate and 1,3-bis (diphenylphosphino)propane (dppp) in toluene at 75°C to afford 2-dimethylamino-4-phenoxy-5-nitropyridine (**10**) in low to moderate yields (10–46%, method A). Chemical yields were not reproducible following this procedure and direct nucleophilic substitution was therefore examined: compound **8** was reacted with dimethylamine under various reaction conditions. In short, although mild S_NAr conditions ($NHMe_2$, THF, or DMF, rt) afforded a mixture of C2/C4 isomers and disubstituted product in a nearly 1:1:1 ratio (CCM analyses), acid-catalyzed conditions and elevated reaction temperature ($NHMe_2$.HCl, DMF, 120°C, method B) allowed regioselective and almost exclusive nucleophilic substitution of the bromine atom that means without concomitant/competitive displacement of the phenoxy group at C4 (Scheme 1). Indeed, it is well established [29,30] that nucleophilic attack on basic α-halo-heterocycles is most often facilitated by acid-catalysis, presumably because it proceeds via the *N*-protonated iminium ion. In our case, even if the presence of an acid dramatically decreases the nucleophilicity of dimethylamine and that elevated temperature (120°C) was needed for completion of the reaction, the acid-catalyzed process proceeded in high yield and strongly favored the C2-isomer (**10**) formation.

Eventually, the preparation of 5-amino-2-chloro-4-phenoxypyridine (**11**), 5-amino-2-bromo-4-phenoxypyridine (**12**), 5-amino-2-fluoro-4-phenoxypyridine (**13**), and N^2,N^2-dimethyl-4-phenoxypyridine-2,5-diamine (**14**) was envisaged. Thus, reduction of nitropyridines **4**, **8**, **9**, and **10** by means of iron dust in acetic acid at room temperature gave aminopyridines **11**, **12**, **13**, and **14**, respectively, in good to excellent yields (Scheme 1).

^{1}H NMR spectra of pyridines **1–14** were recorded, and the data obtained for these disubstituted and trisubstituted pyridines is gathered in Table 1.

Assuming that there is no substantial shift difference between NMR experiments measured in $CDCl_3$ and in CD_2Cl_2, the following observations can be made. Hydrogen

Scheme 2. Possible regioisomers formed with reaction of dimethylamine on bromopyridine **8**.

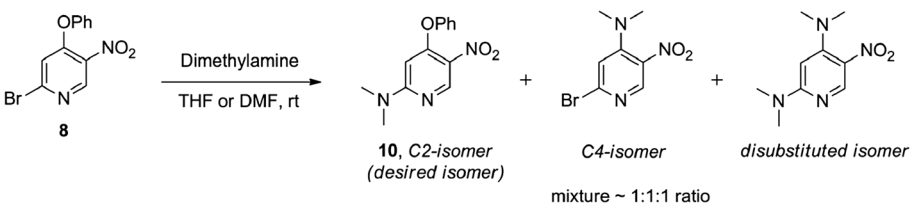
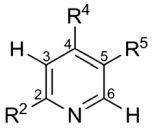


Table 1

^{1}H NMR chemical shift assignments of pyridines (**1–14**).



Compound[a]	Structure			Chemical shifts (δ, ppm)[b]			
	R^2	R^4	R^5	H-6	H-3	H-2	Others
1 [α]	H	Cl	NO_2	9.06 (s)	7.53 (d)[c]	8.63 (d)[c]	—
2 [β]	OH	Cl	NO_2	8.72 (s)	6.69 (s)	—	12.90 (bs, OH)
3 [α]	Cl	Cl	NO_2	8.96 (s)	7.59 (s)	—	—
4 [α]	Cl	OPh	NO_2	8.95 (s)	6.75 (s)	—	7.53 (t, 2H)[f], 7.39 (t, 1H)[f], 7.16 (d, 2H)[f]
5 [α]	OPh	OPh	NO_2	8.83 (s)	6.27 (s)	—	7.50 (t, 2H)[f], 7.41 (t, 2H)[f], 7.35 (t, 1H)[f], 7.25 (t, 1H)[f], 7.22 (d, 2H)[f], 7.10 (d, 2H)[f]
6 [α]	H	OPh	NO_2	9.12 (s)	6.77 (d)[d]	8.53 (d)[d]	7.49 (t, 2H)[f], 7.34 (t, 1H)[f], 7.15 (d, 2H)[f]
7 [β]	OH	OPh	NO_2	8.70 (s)	5.27 (s)	—	12.50 (bs, OH), 7.52 (t, 2H)[f], 7.35 (t, 1H)[f], 7.25 (d, 2H)[f]
7b [β]	OH	OtBu	NO_2	8.66 (s)	7.59 (s)	—	12.20 (bs, OH), 1.28 (s, 9H)
8 [α]	Br	OPh	NO_2	8.90 (s)	6.90 (s)	—	7.52 (t, 2H)[f], 7.39 (t, 1H)[f], 7.15 (d, 2H)[f]
9 [γ]	F	OPh	NO_2	8.86 (s)	6.33 (s)	—	7.50 (t, 2H)[f], 7.40 (t, 1H)[f], 7.19 (d, 2H)[f]
10 [α]	NMe_2	OPh	NO_2	8.99 (s)	5.65 (s)	—	7.45 (t, 2H)[f], 7.27 (t, 1H)[f], 7.13 (d, 2H)[f], 3.05 (s, 6H)
11 [γ]	Cl	OPh	NH_2	7.86 (s)	6.52 (s)	—	7.45 (t, 2H)[f], 7.28 (t, 1H)[f], 7.11 (d, 2H)[f]
12 [α]	Br	OPh	NH_2	7.87 (s)	6.64 (s)	—	7.44 (t, 2H)[f], 7.27 (t, 1H)[f], 7.09 (d, 2H)[f]
13 [γ]	F	OPh	NH_2	7.62 (s)	6.13 (d)[e]	—	7.46 (t, 2H)[f], 7.29 (t, 1H)[f], 7.13 (d, 2H)[f]
14 [γ]	NMe_2	OPh	NH_2	7.77 (s)	5.95 (s)	—	7.39 (t, 2H)[f], 7.17 (t, 1H)[f], 7.07 (d, 2H)[f], 2.86 (s, 6H)

[a]Deuterated solvent used: [α] $CDCl_3$, [β] DMSO-d_6, [γ] CD_2Cl_2.
[b]Signal multiplicity in parentheses.
[c]($^{3}J_{H2–H3} = 5.2$ Hz).
[d]($^{3}J_{H2–H3} = 6.0$ Hz).
[e]($^{3}J_{H–F} = 1.6$ Hz).
[f]($^{3}J_{H–H} = 8.0$ Hz).

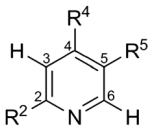
atoms at the 6-position are systematically the most deshielded with ^{1}H NMR signals ranging from 7.62 to 9.12 ppm, because of the vicinal influence of the heterocyclic nitrogen. As expected, the 5-nitro substitution in pyridines leads to H-6 signals much less shielded than those of the corresponding 5-amino pyridines (shift downfield of 1.14 ± 0.09 ppm). ^{1}H NMR signals of hydrogen atoms at the 3-position are detected with great resonance variability. A small shift towards higher fields, of 0.20 to 0.26 ppm, is observed for H-3 signals when the 5-nitro substituent is replaced by a 5-amino group for 2-halo-4-phenoxypyridines (compare **4**, **8**, and **9** to **11**, **12**, and **13**, respectively). The opposite effect was observed in the case of 2-dimethylamino-4-phenoxypyridines **10** and **14**.

Chemical shift values of the ring carbons belonging to synthesized disubstituted and trisubstituted pyridines are listed in Table 2. The NMR signals were assigned unambiguously by sequential analysis of 1D (normal ^{13}C and DEPT135 sequences) and 2D (heteronuclear single quantum correlation HSQC and heteronuclear multiple-bond correlation HMBC) experiments.

In most cases, C-2 and C-4 positions in pyridines are the most deshielded (quaternary phenoxy carbon signal excluded). C-4 resonances occur in a low field window ranging from 162.3 to 137.6 ppm and the C-2 chemical shifts average 155 ppm with the exception of compound **12** whose C-2 is significantly more shielded with a signal at 129.6 ppm. C-3 signals appear invariably at the lowest frequencies with chemical shifts below 130.9 ppm. The carbon atom C-5 bearing the nitro group is consistently observed as a characteristic low-intensity broad signal around 135–130 ppm. Replacement of the electron withdrawing nitro group with the amino substituent, which is π-electron releasing in the *ortho* and *para* positions, at C-5 of the pyridine mainly influences the C-6 chemical shift with a shielding effect (showing behavior similar to that found for H-6) and, to a lesser extent, generates a C-4 signal upfield displacement. Although modifications at position 2 have almost no influence on the C-4 resonance signal, great chemical shift variability is observed for C-2 and C-3 peaks. It is worth noting that, for pyridines bearing a phenoxy at position 4, the more the C-2 signal is shielded, the higher the C-3 signal frequency is.

Table 2

^{13}C NMR chemical shift assignments of pyridines (**1–14**).



Compound[a]	Structure			Chemical shifts (δ, ppm)					
	R^2	R^4	R^5	C-2	C-3	C-4	C-5	C-6	Others
1 [α]	H	Cl	NO_2	146.3	126.5	137.6	144.4	153.0	—
2 [β]	OH	Cl	NO_2	160.5	119.9	138.6	129.5	140.7	—
3 [α]	Cl	Cl	NO_2	155.3	126.6	139.4	143.2	146.6	—
4 [α]	Cl	OPh	NO_2	156.4	111.8	159.5	135.9	147.4	152.2 (C), 130.8 (2CH), 127.2 (CH), 120.8 (2CH)
5 [α]	OPh	OPh	NO_2	167.3	97.8	161.3	133.1	147.3	152.8 (C), 152.5 (C), 130.6 (2CH), 129.7 (2CH), 126.7 (CH), 125.8 (CH), 121.3 (2CH), 121.0 (2CH)
6 [α]	H	OPh	NO_2	154.5	111.8	158.1	136.8	147.4	152.6 (C), 130.6 (2CH), 126.7 (CH), 120.8 (2CH)
7 [β]	OH	OPh	NO_2	163.0	100.7	160.7	125.8	141.3	153.1 (C), 131.0 (2CH), 126.7 (CH), 121.2 (2CH)
7b [β]	OH	OtBu	NO_2	166.6	130.9	148.3	138.7	137.1	80.9 (C), 28.1 ($3CH_3$)
8 [α]	Br	OPh	NO_2	147.0	115.6	158.9	136.3	147.4	152.2 (C), 131.8 (2CH), 127.2 (CH), 120.8 (2CH)
9 [γ]	F	OPh	NO_2	165.9[b]	97.0[c]	162.3[d]	135.3	146.7[e]	153.8 (C), 130.8 (2CH), 127.1 (CH), 120.8 (2CH)
10 [α]	NMe_2	OPh	NO_2	161.8	91.1	160.1	127.8	149.4	152.3 (C), 130.1 (2CH), 125.7 (CH), 120.5 (2CH), 38.1 ($2CH_3$)
11 [γ]	Cl	OPh	NH_2	140.0	110.0	153.3	133.5	135.7	153.8 (C), 130.2 (2CH), 125.5 (CH), 120.3 (2CH)
12 [α]	Br	OPh	NH_2	129.6	113.6	153.0	133.6	136.6	153.7 (C), 130.3 (2CH), 125.6 (CH), 120.3 (2CH)
13 [γ]	F	OPh	NH_2	157.2[f]	95.4[g]	155.4[h]	132.0	132.1[i]	153.8 (C), 130.2 (2CH), 125.6 (CH), 120.4 (2CH)
14 [γ]	NMe_2	OPh	NH_2	155.5	94.7	153.7	125.4	136.2	155.2 (C), 129.8 (2CH), 124.0 (CH), 119.0 (2CH), 38.4 ($2CH_3$)

[a]Deuterated solvent used: [α] $CDCl_3$, [β] DMSO-d_6, [γ] CD_2Cl_2.
[b](d, $J_{C2\text{-}F}$ = 243 Hz).
[c](d, $J_{C3\text{-}F}$ = 43 Hz).
[d](d, $J_{C4\text{-}F}$ = 13 Hz).
[e](d, $J_{C6\text{-}F}$ = 20 Hz).
[f](d, $J_{C2\text{-}F}$ = 240 Hz).
[g](d, $J_{C3\text{-}F}$ = 46 Hz).
[h](d, $J_{C4\text{-}F}$ = 10 Hz).
[i](d, $J_{C6\text{-}F}$ = 18 Hz).

CONCLUSION

A series of disubstituted and trisubstituted pyridines has been synthesized (**2–14**) and fully characterized by ^{1}H and ^{13}C NMR experiments. It was shown that when dimethylamine is used as nucleophile on 2,4-disubstituted-5-nitropyridines, it is possible to regioselectively favor the C-2 substitution over the C-4 displacement even if the latter carbon is the most activated position. The observed changes in the chemical shifts upon substitution are rather significant and might be interpreted in terms of inductive and mesomeric effects. The electron-density distribution in these pyridine systems can also give some insight in the reactivity of the different substituted carbons toward nucleophilic displacements. The halo-pyridines synthesized may offer cross-coupling reaction opportunities, whereas the 5-amino substituent provide the possibility to design more complex structures via, for example, reductive amination or peptide bond formation and thus constitute interesting building blocks for the preparation of a broad range of chemicals. The experimental ^{1}H and ^{13}C chemical shifts of pyridines **1–14** collected and reported herein constitute a valuable database for, as an example, testing the accuracy of different NMR chemical shift calculation programs by comparison of the predicted and experimental values [31].

EXPERIMENTAL

Chemicals were purchased from Aldrich France and were used without further purification, unless otherwise stated. Flash chromatographies were conducted on silica gel or alumina gel (0.63–0.200 mm, VWR) columns. TLCs were run on precoated plates of silica gel $60F_{254}$ (VWR). The compounds were localized at 254 nm using a UV lamp and/or by dipping the TLC plates in a 1% ethanolic ninhydrin solution, a basic $KMnO_4$ aqueous solution or a 1% MeOH/H_2O (1/1, v:v) $FeCl_3$ solution and heating on a hot plate. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker

(Wissembourg, France) Avance 400 MHz apparatus, and chemical shifts were referenced to the hydrogenated residue of the deuterated solvent ($\delta[CDHCl_2] = 5.32$ ppm and $\delta[CHCl_3] = 7.23$ ppm) for ^{1}H NMR and to the deuterated solvent ($\delta[CD_2Cl_2] = 53.5$ ppm and $\delta[CDCl_3] = 77.0$ ppm) for ^{13}C NMR experiments. The standard concentration of the analyzed samples was 20 mg/mL. The chemical shifts are reported in ppm, downfield from TMS (s, d, t, and b for singlet, doublet, triplet, and broad, respectively). Complete ^{1}H and ^{13}C NMR spectra assignments for compounds **1–14** are summarized in Tables 1 and 2, respectively. The high resolution mass spectrometry (HRMS) analyses were performed by Imagif (ICSN-CNRS, Gif-sur-Yvette) by electrospray with positive (ESI +) or negative (ESI-) ionization mode.

4-Chloro-5-nitropyridin-2-ol (2). A cold solution (0–5°C) of commercial 4-chloro-3-nitropyridine (**1**) (2 g, 12.6 mmol) and *t*-BuOOH (2.53 mL, 6 M solution in decane, 15.2 mmol) in DMF (10 mL) was added slowly via cannula to a solution of *t*-BuOK (37.8 mmol) in DMF (10 mL) at −35°C. The reaction mixture was stirred for 2 h at −35°C and diluted with a saturated aqueous solution of NH_4Cl (50 mL). Stirring was prolonged for 30 min at room temperature, and the solution basified to pH 8–9 with a saturated aqueous solution of K_2CO_3 and washed with Et_2O. The aqueous layer was acidified to pH 1 and extracted twice with Et_2O. The combined organic layers were evaporated to dryness, and the residue triturated in MeOH. The precipitate was filtered to afford pure compound **2** (1.12 g, 51%) as yellow crystals. R_f 0.14 (CH_2Cl_2/acetone 9/1); HR-ESI(−)-MS *m/z* Calcd for $C_5H_3ClN_2O_3$: 172.9754 $[M-H]^-$, found 172.9751.

2,4-Dichloro-5-nitropyridine (3). Phosphorous oxychloride (2.61 mL, 28.4 mmol) was added to a suspension of 4-chloro-5-nitropyridin-2-ol (**2**) (1.65 g, 9.5 mmol) in toluene (50 mL), and the heterogeneous mixture was refluxed for 6 h. The reaction was cooled to 0°C, and a saturated aqueous solution of K_2CO_3 was carefully added. The resulting mixture was extracted twice with ethyl acetate. The combined organic layers were successively washed with water and brine, dried over Na_2SO_4 and evaporated to dryness. The resulting syrup was purified by silica gel column chromatography (heptane/EtOAc 16/1) to afford expected compound **3** (1.32 g, 72%) as light-yellow crystals. R_f 0.81 (CH_2Cl_2/acetone 9/1); ESI(+)-MS (*m/z*): not detected.

2-Chloro-5-nitro-4-phenoxypyridine (4).

Method A (from 2,4-dichloro-5-nitropyridine (3)). To a solution of 2,4-dichloro-5-nitropyridine (**3**) (0.89 g, 4.62 mmol) and NaH (133 mg, 5.54 mmol) in THF (30 mL) was added dropwise a solution of phenol (454 mg, 5.54 mmol) in THF (10 mL). The reaction mixture was stirred overnight at room temperature, diluted with EtOAc, and washed successively with a saturated aqueous solution of K_2CO_3 (twice), water, and brine. The organic layer was dried over Na_2SO_4, evaporated to dryness, and the resulting residue purified by silica gel column chromatography (CH_2Cl_2 100%) to afford undesired 2,4-diphenoxy-5-nitropyridine (**5**) (128 mg, 9%) and desired compound **4** (786 mg, 68%) as white crystalline solids. Compound **4**: R_f 0.59 (heptane/EtOAc 2/1); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_7ClN_2O_3$: 251.0223 $[M+H]^+$, found 251.0216. Compound **5**: R_f 0.62 (heptane/EtOAc 2/1); HR-ESI(+)-MS *m/z* Calcd for $C_{17}H_{12}N_2O_4$: 309.0875 $[M+H]^+$, found 309.0877.

Method B (from 5-nitro-4-phenoxypyridin-2-ol (7)). Phosphorous oxychloride (1.07 g, 6.96 mmol) was added to a suspension of 5-nitro-4-phenoxypyridin-2-ol (**7**) (538 mg, 2.32 mmol) in toluene (10 mL), and the heterogeneous mixture was refluxed for 2 h. The reaction was cooled to 0°C and carefully diluted with a saturated aqueous solution of K_2CO_3 and extracted twice with EtOAc. The combined organic layers were successively washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The resulting brownish residue was purified by silica gel column chromatography (heptane/EtOAc 9/1) to afford expected compound **4** (371 mg, 64%) as white crystals.

3-Nitro-4-phenoxypyridine (6). Starting from commercial 4-chloro-3-nitropyridine (**1**) (5.0 g, 31.6 mmol), the synthesis was performed in the same manner as described for the preparation of **4** (method A). Compound **6** was obtained quantitatively (6.8 g, 100%) as a white solid and was pure enough to be used in the next step without further purification. R_f 0.22 (heptane/EtOAc 2/1); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_8N_2O_3$: 217.0613 $[M+H]^+$, found 217.0608.

5-Nitro-4-phenoxypyridin-2-ol (7). Starting from 3-nitro-4-phenoxypyridine (**6**) (6.8 g, 31.5 mmol), the synthesis was performed in the same manner as for the preparation of compound **2**. Compound **7** (3.28 g, 45%) was isolated as a beige powder and trituration of the evaporated filtrate with CH_2Cl_2 afforded an insoluble beige solid that was isolated and identified as 5-nitro-4-*tert*-butoxypyridin-2-ol (**7b**) (217 mg, 15%). Compound **7**: R_f 0.18 (CH_2Cl_2/acetone 8/2); HR-ESI(−)-MS *m/z* Calcd for $C_{11}H_8N_2O_4$: 231.0406 $[M-H]^-$, found 231.0414. Compound **7b**: R_f 0.07 (CH_2Cl_2/acetone 8/2); HR-ESI(+)-MS *m/z* Calcd for $C_9H_{12}N_2O_4$: 213.0875 $[M+H]^+$, found 213.0865.

2-Bromo-5-nitro-4-phenoxypyridine (8). Phosphorous oxybromide (6.10 g, 16.0 mmol) was added to a suspension of 5-nitro-4-phenoxypyridin-2-ol **7** (1.24 g, 5.34 mmol) in toluene (60 mL), and the heterogeneous mixture was refluxed for 2 h. The reaction was cooled to 0°C and carefully diluted with a saturated aqueous solution of K_2CO_3 and extracted twice with EtOAc. The combined organic layers were successively washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The resulting brownish residue was purified by silica gel column chromatography (heptane/EtOAc 9/1) to afford expected compound **8** (1.28 g, 81%) as white crystals. R_f 0.73 (CH_2Cl_2/acetone 9/1); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_7BrN_2O_3$: 294.9718 $[M+H]^+$, found 294.9717.

2-Fluoro-5-nitro-4-phenoxypyridine (9). To a solution of 5-nitro-4-phenoxypyridin-2-ol (**7**) (680 mg, 2.93 mmol) in acetonitrile (25 mL) was added dropwise a 1 M solution of (diethylamino)sulfur trifluoride (DAST, 1.55 mL, 11.7 mmol) in CH_2Cl_2. The resulting mixture was stirred for 6 h at 75°C and was then diluted with water and extracted twice with EtOAc. The organic layers were combined and washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc 9/1) to give expected compound **9** (300 mg, 44%) as a light-yellow syrup and recovered starting material (230 mg). R_f 0.62 (petroleum ether/Et_2O 2/1); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_7FN_2O_3$: 235.0519 $[M+H]^+$, found 235.0522.

***N,N*-Dimethyl-5-nitro-4-phenoxypyridin-2-amine (10)**.

Method A (Buchwald–Hartwig amination). A mixture of 2-bromo-5-nitro-4-phenoxypyridine (**8**) (500 mg, 1.69 mmol), Pd $(OAc)_2$ (38 mg, 0.17 mmol), 1,3-*bis*(diphenylphosphino)propane (140 mg, 0.34 mmol), dimethylamine (1.02 mL, 2.03 mmol, 2 M solution in THF), *t*-BuOK (266 mg, 2.37 mmol), and toluene (10 mL) was stirred and heated to 70°C until complete disappearance of compound **8**. The mixture was then poured into water and extracted twice with EtOAc. The combined organic layers were successively washed with a saturated aqueous solution of K_2CO_3, a 1 M aqueous HCl solution, and brine before being

dried over Na_2SO_4, filtered and evaporated to dryness. The dark residue was purified by silica gel column chromatography (Petroleum ether/EtOAc 9/1) to afford compound **10** (200 mg, 46%) as yellow needles. R_f 0.26 (petroleum ether/Et_2O 7/3); HR-ESI(+)-MS *m/z* Calcd for $C_{13}H_{13}N_3O_3$: 260.1035 $[M+H]^+$, found 260.1030.

Method B (amination via acid-catalyzed/elevated temperature conditions). To a solution of 2-bromo-5-nitro-4-phenoxypyridine (**8**) (2.15 g, 7.29 mmol) in DMF (40 mL) was added $NHMe_2$.HCl (713 mg, 8.75 mmol) in one portion, and the reaction mixture was stirred at 120°C for 16 h. The mixture was partitioned between EtOAc and water, the organic layer was collected and washed with brine before being dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by silica gel column chromatography (heptane/EtOAc 7/3) to afford desired compound **10** (1.55 g, 82%) as yellow needles.

2-Chloro-4-phenoxypyridin-5-amine (11). A mixture of 2-chloro-5-nitro-4-phenoxypyridine (**4**) (200 mg, 0.80 mmol) and powdered Fe (270 mg, 2.40 mmol) in acetic acid (4 mL) was stirred for 30 min at 90°C. The resulting mixture was diluted with water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting syrup was purified by silica gel column chromatography (heptane/EtOAc 3/1) to afford desired compound **11** (170 mg, 96%) as a light-yellow oil. R_f 0.20 (petroleum ether/Et_2O 2/1); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_9ClN_2O$: 221.0482 $[M+H]^+$, found 221.0482.

2-Bromo-4-phenoxypyridin-5-amine (12). Starting from 2-bromo-5-nitro-4-phenoxypyridine (**8**) (240 mg, 0.81 mmol), the synthesis was performed in the same manner as for the preparation of compound **11**. Compound **12** (210 mg, 98%) was isolated after silica gel column chromatography (heptane/EtOAc 3/1) as a light-yellow syrup. R_f 0.19 (petroleum ether/Et_2O 7/3); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_9BrN_2O$: 264.9976 $[M+H]^+$, found 264.9979.

2-Fluoro-4-phenoxypyridin-5-amine (13). Starting from 2-fluoro-5-nitro-4-phenoxypyridine (**9**) (300 mg, 1.28 mmol), the synthesis was performed in the same manner as for the preparation of compound **11**. Compound **13** (185 mg, 71%) was isolated after silica gel column chromatography (heptane/EtOAc 3/1) as a light-yellow oil. R_f 0.24 (petroleum ether/Et_2O 2/1); HR-ESI(+)-MS *m/z* Calcd for $C_{11}H_9FN_2O$: 205.0777 $[M+H]^+$, found 205.0788.

N^2,N^2-Dimethyl-4-phenoxypyridine-2,5-diamine (14). Starting from *N,N*-dimethyl-5-nitro-4-phenoxypyridin-2-amine (**10**) (200 mg, 0.77 mmol), the synthesis was performed in the same manner as for the preparation of compound **11**. Compound **14** (130 mg, 74%) was isolated after silica gel column chromatography (Petroleum ether/EtOAc 1/1) as pink crystals. R_f 0.30 (toluene/acetone 1/1); HR-ESI(+)-MS *m/z* Calcd for $C_{13}H_{15}N_3O$: 230.1293 $[M+H]^+$, found 230.1295.

Acknowledgment. The authors also wish to thank Dr Dirk Roeda for proof reading the manuscript and suggesting linguistic corrections. This work was supported in part by the EC-FP6-project DiMI (LSHB-CT-2005-512146).

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