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Furo[3,2-*b*]pyridine: a convenient unit for the synthesis of polyheterocycles

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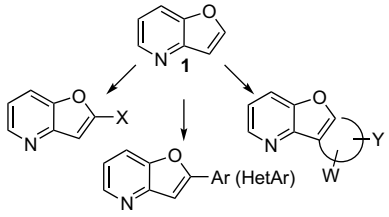
ABSTRACT

An efficient and rapid synthesis of furo[3,2-*b*]pyridine **1** is described using a one-pot Sonogashira coupling/heteroannulation sequence. Regioselective lithiation of this synthon was performed leading to various 2-substituted furo[3,2-*b*]pyridines. Some of them were used as substrates for short functional synthesis of polyheterocycles.

1. Introduction

Combining a π-electron rich furan ring and a π-electron deficient pyridine ring, furopyridines are of general interest because of their characteristic reactivity resulting from the annulation. These fused aromatic heterocycles seem to have especially attracted much attention as pharmacophore units due to their isosterism with benzofurans, indoles or azaindoles, which are important moieties in many biological active compounds.[1–3] In our ongoing research to develop new efficient access to heterocyclic synthons as versatile precursors of polyheterocyclic derivatives,[4–6] we focused our attention on the furo[3,2-*b*]pyridine **1** among the six isomeric series of furopyridine framework ([*b*]-, [*c*]- or [*f*]-fused heterocycles). Advantages of this scaffold are to allow further selective functionalizations, which could be envisioned using regioselective reactions on furan moiety or/and on pyridinic ring such as metallation/halogenation, cross-coupling, arylamination, hydroxyamination, dihydroxylation, epoxidation… (Scheme 1).

To our knowledge, only a few papers described the preparation of unsubstituted furo[3,2-*b*]pyridine **1**.[7–10] According to the general strategy of producing fused heterocycles, Gronowitz and colleagues[7] reported the preparation of **1** by using a Friedländer reaction as main step to realize the construction of the pyridinic ring from 3-amino-2-formylfuran. Hickson and McNab proposed a one-step formation of pyridine ring by high-vacuum pyrolysis of *O*-methyloxime of furylaldehyde.[8] In 1986 a multistep strategy



Scheme 1. Furo[3,2-*b*]pyridine **1**, precursor of polyheterocycles.

based on the formation of the furan ring was proposed by Shiotani and Morita[9] starting from the 3-hydroxypyridine-2-carboxylate preformed ring. Despite their interest, these methods suffer from disadvantage of the limited access to starting materials, long-multistep sequences and/or low overall yields.

In contrast, a number of synthetic approaches to the 2- or 3-substituted or 2,3-disubstituted furo[3,2-*b*]pyridines have been described in the literature. Various strategies are reported[10] such as, for example, a carbanionic ring closure to prepare 3-vinyl-furo[3,2-*b*]pyridine,[11] a photocyclization of 3-furanyl-3-amino-alkene imines[12] or a heteroaromatic C–H insertion of alkylidenecarbene.[13] Nevertheless, the most reported processes used a Pd-catalyzed heteroannulation of internal alkynes.[14] Such processes allowed the ring construction of benzofuran, indole, azaindole or thienopyridine…[4,15] Starting from halogeno- or internal alkynylpyridinols the synthesis of substituted furo[3,2-*b*]pyridinic moieties was then envisioned by Arcadi and Cacchi as well as by Larock groups.[16–18] In 2002, Arcadi and colleagues proposed an interesting alternative sequence using an unsubstituted

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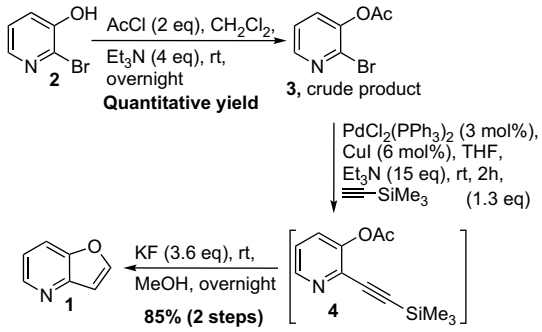
alkynylpyridinol as substrate and an appropriate aryl halide or a substituted vinyl triflate.[19] According to this method, numerous 2-substituted furo[3,2-*b*]pyridines were obtained in moderate to good yields. However, it must be noted that this process appeared as limited for the introduction of aryl groups and furo[3,2-*b*]pyridine **1** was always observed as by-product.

In this context, we report here an improved and rapid synthesis of the furo[3,2-*b*]pyridine **1** as well as the preparation of various functional derivatives and fused heterocycles resulting from a selective lithiation-functionalization sequence and cross-coupling reactions.

2. Results and discussion

It is well known that *o*-hydroxyalkynylpyridines are not stable and cyclize spontaneously to give substituted furopyridines.[16–18] We envisioned to exploit this result and we proposed an one-pot synthesis of furo[3,2-*b*]pyridine **1** based on the approach described by Arcadi and colleagues.[19] As outlined in Scheme 2, the preparation of the expected fused heterocycle **1** required a Sonogashira coupling of the *O*-protected-2-bromopyridinol **3** and trimethylsilylacetylene under palladium catalysis ($PdCl_2(PPh_3)_2$, 3 mol %) in the presence of a catalytic amount of CuI (6 mol %).[20] Contrary to the latter reports, 3-*O*-acetoxy-2-trimethylsilanylethynylpyridine **4** was not isolated and we realized the removal of both acetyl and trimethylsilyl groups by potassium fluoride in methanol as solvent. In these conditions, the furo[3,2-*b*]pyridine **1** was obtained in excellent overall yield (85%) from commercially available 2-bromopyridin-3-ol. This three-step procedure can easily be scaled-up (until ca. 11 g of **1**) without intermediate purifications.[21]



Scheme 2. Efficient synthesis of furo[3,2-*b*]pyridine **1**.

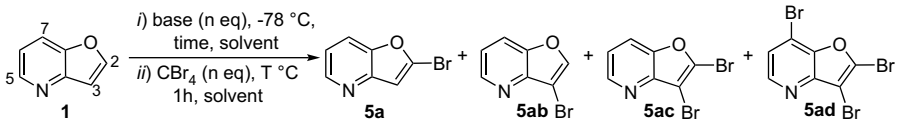
As previously mentioned, the furopyridinyl framework **1** displays a great synthetic interest because of the chemical properties of each cycle. With regard to the literature, substitution of the pyridinyl ring required an N-activation of furopyridine,[22] and only a few reactions involving the furan ring are described such as nitration, bromination…[23] Disadvantage of these processes was to restrict the diversity of introduced groups.

With the purpose of preparing a large and various 2-substituted furo[3,2-*b*]pyridine family, which presents a great synthetic potential, we envisioned to examine the functionalization of **1** by a one-pot lithiation/electrophilic quenching sequence. The metallation of the furo[3,2-*b*]pyridine units displays a great interest because of the four potential lithiated positions, H-2, H-3, H-5 and H-7. To be noted that the synthesis of 2-formyl and 2-phenylthiofuro[3,2-*b*]pyridines were reported at −78 °C using *n*-butyllithium (*n*-BuLi) as base. Yields varied from 45 to 55% (in our hands) and no addition of *n*-BuLi to the pyridine ring was observed.[24] Therefore, we decided to improve and extend the metallation of furo[3,2-*b*]pyridine **1** and to evaluate the influence of base on the regioselectivity. We report in Table 1 the more significant results of this preliminary study. All the reactions were monitored by GC using internal standard method. At first, the lithiation of derivative **1** was carried out with 1 equiv of *n*-BuLi, at −78 °C for 1 h, in THF followed by treatment with CBr_4 (as representative electrophile) in THF, at −95 °C for 1 h. These conditions did not produce a total conversion of the substrate (only 77%). Nevertheless, only 2-bromofuro[3,2-*b*]pyridine **5a** was detected in 77% yield (GC), without any trace of the 3-bromo isomer **5ab** or isomers **5ac**–**5ad** (entry 1). To increase the conversion yield, 2 equiv of *n*-BuLi at −78 °C for 1 h in anhydrous THF was required for the metallation (entries 2 and 3, 94 and 100%, respectively). The expected 2-bromofuro[3,2-*b*]pyridine **5a** was then obtained in a 89% yield in the presence of some traces of **5ab**. In these experiments, the condensation temperature (−95 °C) was of great importance since under less cryogenic conditions (−78 °C) the formation of only 69% of **5a** was observed. At this latter temperature, reaction conducted to intractable mixture probably resulting from Br/Li exchange, halogen dance and/or elimination. Finally, a larger excess of base did not allow us to increase the reaction yield since **5a** was detected in 90% yield in the presence of 2,3-dibromo heterocycle **5ac** (7% yield) when 3 equiv of *n*-BuLi was used (entry 4). To succeed in a regioselective bromination in 2-position of **1**, the more appropriate conditions then required a metallation/functionalization sequence using 2 equiv of *n*-BuLi in THF at −78 °C and an electrophilic condensation at −95 °C. In these conditions, the reaction is highly selective in **5a** and by-product **5ab** or **5ac** is produced as traces (easily removed by a simple column chromatography). However, these by-products could be of interest in a synthetic purpose and we decided to explore other lithiating agents, which could favour their formations. If **5ab** resulted from a direct lithiation of **1**, a pyridino-directing basic system might be useful for a deprotonation at C-3 position.

Some of our previous investigations[25] exhibited the usefulness of the monometallic [*n*-BuLi/LiDMAE] superbase (DMAE: 2-(dimethylamino)ethanol) in apolar solvents to perform regioselective lithiation in α-position of pyridine nitrogen atom. Deprotonation at C-5 by treatment with the superbase [*n*-BuLi/LiDMAE] could be suggested involving a chelating directed lithiation while deprotonation at C-3 could be envisioned involving a pyridino-directed lithiation. Taking into account the relative acidity of H-5 and H-3, the metallation of the pyridinic ring appears less probable than a C-3 lithiation. This was confirmed by experience since only **5a** and **5ab** were obtained whatever the solvent used (toluene or Et_2O). In toluene, the formation of **5ab** was favoured but **5a** remained the major product (entry 5). The overall conversion was increased in Et_2O with a similar initial reaction progress conducting to a **5a**–**5ab** mixture (entry 6). However, in this coordinating solvent (compare to toluene), the lithiated species conducting to **5ab** seemed unstable since for an extended reaction time only **5a** was obtained (entry 7). This led us to conclude that 3-lithio derivative is unstable and that the classical oxygen induced Directed *ortho*-Metallation (DOM) seems stronger than the expected pyridino-directed one in coordinating solvent.

We next turned our investigations on LiTMP[26] induced metallation with the aim to favour the **5ac** formation. We found that 3 equiv of LiTMP was required to obtain a complete conversion of starting material **1** and **5ac** became the major product (entries 8 and 9). When the condensation temperature was held at −95 °C (entry 9), the 2,3,7-tribromofuro[3,2-*b*]pyridine **5ad** was detected in 25% yield in mixture with the 2,3-dibromo derivative **5ac** as main product (50% yield) and 2-bromofuropyridine **5a** in 14% yield. As revealed by GC-monitoring, H-2, H-3 and H-7 seem to be replaced successively in order of their acidity during an evolving process due to the excess of basic system. A larger excess of LiTMP (entry 10 or 11) favoured the polyfunctionalization sequence producing **5ad** as the major reaction product (entry 11). Interestingly, the yield of **5ad**

Table 1
Lithiation of furo[3,2-*b*]pyridine **1**



Entry	Metallation conditions	Condensation conditions	Conversion[a,b] (%)	Yields[a,b] (%)
	Base (equiv)/solvent/time	Solvent/*T* (°C)/CBr_4 (equiv)		**5a**/**5ab**/**5ac**/**5ad**
n-BuLi/THF/1 h				
1	1 equiv	THF/−95 °C/1 equiv	77	77/0/0/0
2	2 equiv	THF/−95 °C/2 equiv	94	89/3/0/0
3	2 equiv	THF/−78 °C/2 equiv	100	69/Trace/5/0
4	3 equiv	THF/−95 °C/3 equiv	100	90/Trace/7/0
[*n*-BuLi/LiDMAE]				
5	3 equiv/toluene/1 h	THF/−95 °C/3 equiv	73	20/9/0/0
6	3 equiv/Et_2O/1 h	Et_2O/−95 °C/3 equiv	80	30/20/0/0
7	3 equiv/Et_2O/2 h	Et_2O/−95 °C/3 equiv	95	47/Trace/0/0
LiTMP/THF/1 h				
8	3 equiv	THF/−78 °C/3 equiv	100	15/Trace/49/14
9	3 equiv	THF/−95 °C/3 equiv	100	14/0/50/25
10	4 equiv	THF/−95 °C/4 equiv	100	0/0/25/52
11	6 equiv	THF/−95 °C/6 equiv	100	0/0/Trace/46
12	6 equiv	THF/−95 °C/9 equiv	100	0/0/Trace/54

[a] Reaction performed on 1.2 mmol of furo[3,2-*b*]pyridine **1**.
[b] GC yields determined by internal standard method.

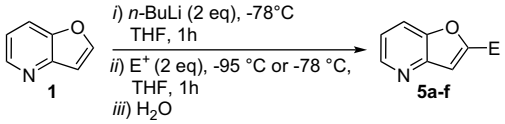
was increased in the presence of 6 equiv of LiTMP and 9 equiv of electrophile (3 equiv per site of functionalization) of electrophile (entry 12).

As summary, this preliminary study showed that 2-functionalization of **1** is selectively produced by a lithiation process using *n*-BuLi while di- or tribrominated derivatives can be obtained by reactions carried out with LiTMP.

In a synthetic purpose, we next decided to extend the *n*-BuLi induced functionalization by examining the reactivity of various electrophiles (Table 2). Derivatives **5b**–**f** were then prepared in good to excellent yields (70–95%) starting from furo[3,2-*b*]pyridine **1**. Since a −95 °C condensation temperature was required for the efficient preparation of **5a** and **5e**, we noted that 2-substituted furo[3,2-*b*]pyridines **5b**, **5c**, **5d** and **5f** could also be obtained at −78 °C (condensation temperature). Due to the less *ortho*-directing effect of the introduced substituents, the formed products appear stable in the reaction medium under less cryogenic conditions.

From these results, we next explored the preparation of 2-aryl, 2-heteroaryl and especially 2-vinyl and 2-alkynylfuro[3,2-*b*]pyridines **6**–**11** by reaction sequences involving various Pd-catalyzed cross-coupling (Stille, Sonogashira or Suzuki reactions) starting from derivative **5a** or **5e** (Table 3).

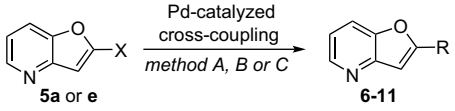
Table 2
Preparation of 2-substituted furo[3,2-*b*]pyridines **5a**–**f**

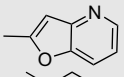
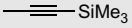
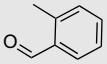


	E	Yields[a,b] (%)		E	Yields[a,b] (%)
5a	Br	76	**5d**[c]	$SiMe_3$	70
5b[c]	CH(OH)Ph	95	**5e**[d]	$SnBu_3$	84
5c[c]	SMe	89	**5f**[c]	CHO	85

[a] Reactions performed on 1.2 mmol of furo[3,2-*b*]pyridine **1**.
[b] Isolated yields after silica gel chromatography.
[c] Condensation was performed at −78 °C.
[d] Condensation was performed for 15 min.

Table 3
Preparation of 2-aryl, 2-heteroaryl, 2-vinyl or 2-alkynyl furo[3,2-*b*]pyridines **6**–**11**



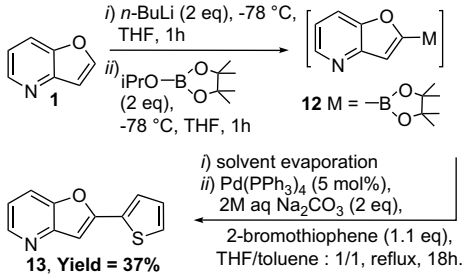
Substrate	Product	R	Method	Yields[a,b] (%)
5e (X=$SnBu_3$)	**6**		A	92
5e (X=$SnBu_3$)	**7**		A	50
5e (X=$SnBu_3$)	**8**		A	62
5a (X=Br)	**9**		B	87
5a (X=Br)	**10**		A	83
5a (X=Br)	**11**		C	91

[a] Reactions performed on 0.50 or 5.05 mmol of furo[3,2-*b*]pyridine **5a** or **5e**.
[b] Isolated yields after silica gel chromatography. Method A: **5e** or CH_2=$CHSnBu_3$ (1.1 equiv), HetArBr or **5a** (1.0 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), DMF, 110 °C, 2 h. Method B: **5a** (1.0 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), trimethylsilylacetylene (1.3 equiv), THF, Et_3N (15 equiv), rt, 12 h. Method C: **5a** (1.0 equiv), *o*-$(CHO)C_6H_4B(OH)_2$ (1.3 equiv), Na_2CO_3 2 M aqueous solution (2.0 equiv), $Pd(PPh_3)_4$ (5 mol %), THF, reflux, 3 h.

The [2,2′]bi[furo[3,2-*b*]pyridinyl] **6** was easily prepared in excellent yield (92%) starting from stannanylfuro[3,2-*b*]pyridine **5e** and 2-bromofuro[3,2-*b*] pyridine **5a**, in the presence of palladium catalyst ($Pd(PPh_3)_2Cl_2$, 5 mol %) and in DMF as solvent (Method A). The same catalyst system was used to perform the synthesis of pyridinyl derivatives **7** and **8** starting from **5e** in 50 and 62% yields, respectively. Both heteroaryl compounds **7** and **8** were obtained in mixture with symmetric derivative **6** (17 and 19% isolated yields,

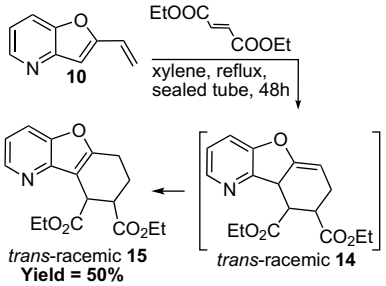
respectively) resulting from homocoupling of **5e**. Vinyl analogue **10** was yielded in 83% according to a similar procedure using the bromide **5a** and vinyltributyltin. We also succeeded in introducing an alkynyl unit using a Sonogashira coupling starting from bromide **5a** and trimethylsilylacetylene in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %) and CuI (10 mol %), in a mixture of THF/Et_3N. The desired alkynyl furo[3,2-*b*]pyridine **9** was then obtained in very good yield (87%). A Suzuki coupling reaction starting from bromide **5a**, 2-formylbenzeneboronic acid as reagent in the presence of $Pd(PPh_3)_4$ as catalyst allowed to prepare the 2-formylarylfuro[3,2-*b*]pyridine **11** in excellent yield (91%).

As depicted in Scheme 3, reaction of the 2-lithiofuro[3,2-*b*]pyridine with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane proceeded efficiently within 1 h at −78 °C in THF to give the boronic intermediate [**12**] (total conversion was confirmed by GC-monitoring). After evaporation of THF, intermediate [**12**] reacted under the current Suzuki coupling conditions in the presence of 2-bromothiophene to provide the expected heteroaromatic derivative **13** in 37% overall yield starting from **1** and furopyridine **1** (15% yield) was recovered resulting from deborylation of [**12**].



Scheme 3. Metallation/Suzuki coupling reaction: preparation of 2-thiophenylfuro[3,2-*b*]pyridines **13**.

Among the many approaches to fused polyheterocycles, the Diels–Alder [4+2] cycloaddition plays a significant role. Our synthetic strategy directed toward the expected tetrahydrobenzo[4,5]furo[3,2-*b*]pyridine envisioned a sequence consisting of a Stille coupling followed by a Diels–Alder cycloaddition (Scheme 4). Then, we envisioned a sequential way to the desired polyheterocycle **15** using a Diels–Alder reaction from vinyl heteraryl compound **10** and fumarate diester, in xylene. After refluxing in sealed tube for 48 h, the tetrahydrobenzo[4,5]furo[3,2-*b*]pyridine **15** was isolated in 50% yield without any trace of isomer **14**. In the reaction conditions, isomerization of the double bond occurred as confirmed by spectroscopic data.



Scheme 4. Synthesis of 6,7,8,9-tetrahydrobenzo[4,5]furo[3,2-*b*]pyridine **15**.

Surprisingly, the same reaction performed with maleic anhydride as dienophile was inefficient. The most part of starting material was recovered. Since comparable cycloaddition has been performed under hyperbaric conditions,[27] the stability of the cycloadduct could be questioned and the retro-Diels–Alder reaction was favoured due to conformational restrictions of the formed four fused polyheterocycle. From this hypothesis, the 50% isolated yield in **15** appears of interest.

3. Conclusion

In summary, we have described the convenient and efficient large scale synthesis of furo[3,2-*b*]pyridine **1** in excellent overall yield (85%) using a tandem Sonogashira coupling/heteroannulation reaction as main step. Our main efforts have next been devoted to the versatile functionalization of the heteroaromatic system using efficient sequences. We succeeded in preparing various 2-aryl, 2-heteroaryl, 2-vinyl or 2-alkynyl heterocycles in good overall yield (37–72%) starting from furo[3,2-*b*]pyridine **1**.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded at 400 or 250 and 100 MHz, respectively, with $CDCl_3$ as solvent and TMS as internal standard (for ^1H NMR). HRMS spectra were recorded on a BRUKER micrOTOF-Q spectrometer at the Service Commun of the Jean Barriol Institute of Nancy. MS were recorded on a SHIMADZU GCMS-QP2010 spectrometer. Melting temperatures are uncorrected.

4.2. Materials and solvents

All reagents were commercially available and were purified by distillation when necessary. *n*-BuLi was used as a commercial 1.6 M solution in hexanes. 2-(Dimethylamino)ethanol (DMAE) was distilled and stored over molecular sieves before use. Toluene, xylene and THF were distilled and stored on sodium wire before use. Column chromatography purification was performed on silica gel (Geduran Si 60, 0.0063–0.200 nm).

4.3. Acetic acid 2-bromopyridin-3-yl ester (3)

To a solution of 2-bromo-3-hydroxypyridine (10.00 g, 57.5 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) in presence of Et_3N (32 mL, 230.0 mmol, 4.0 equiv) was added dropwise a solution of acetyl chloride (8.17 mL, 115.0 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) at 0 °C, under argon atmosphere. The reaction medium was stirred overnight at room temperature. After filtration and hydrolysis performed with H_2O (2×100 mL), the aqueous phase was then extracted with ethyl acetate (AcOEt) (3×50 mL). The combined organic layers were dried over magnesium sulfate ($MgSO_4$). After filtration and solvent evaporation, the crude product was quickly filtered on silica gel to eliminate triethylamine salts. The expected acetic acid 2-bromopyridin-3-yl ester **3** (12.36 g) was then obtained as an oil in quantitative yield. Spectroscopic data are in conformity with the literature.[21]

4.4. Furo[3,2-*b*]pyridine (1)

To a suspension of $PdCl_2(PPh_3)_2$ (2.3 g, 3.3 mmol, 3 mol %) and CuI (1.25 g, 6.6 mmol, 6 mol %) in THF (500 mL), in presence of Et_3N (228 mL, 1.64 mol, 15.0 equiv), was added in one portion 2-bromopyridinyl compound **3** (23.60 g, 109.2 mmol, 1.0 equiv) and trimethylsilylacetylene (13.92 g, 142.0 mmol, 1.3 equiv) in THF (100 mL) under argon atmosphere. Then, the reaction medium was stirred for 2 h at room temperature. After rapid filtration and solvent evaporation, the mixture was diluted with MeOH (250 mL) and potassium fluoride (22.80 g, 393.1 mmol, 3.6 equiv) was added

portionwise over 20 min. After stirring overnight at room temperature, filtration on Celite and evaporation of MeOH, the crude product was solubilized in ethyl acetate (300 mL), washed with H_2O (140 mL) and the aqueous layer was extracted with AcOEt (3×60 mL). The combined organic layers were then washed with aqueous saturated Na_2SO_3 solution (200 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography (eluent: hexane/AcOEt 7:3) and led to the expected furo[3,2-*b*]pyridine **1** (11.05 g, 85%) as an orange oil. Spectroscopic data are in conformity with the literature.[8]

4.5. Preparation of 2-substituted furo[3,2-*b*]pyridines (5a–f)

To a solution of furo[3,2-*b*]pyridine **1** (143 mg, 1.2 mmol, 1.0 equiv) in THF (15 mL) was added dropwise *n*-BuLi (1.5 mL, 2.4 mmol, 2.0 equiv) at −78 °C, under argon atmosphere. After stirring for 1 h at −78 °C, the appropriate electrophile (2.4 mmol, 2.0 equiv) was added in THF (5 mL) at −78 °C or −95 °C. After stirring for 15 min or 1 h, the hydrolysis was performed with H_2O (10 mL) at the condensation temperature. The aqueous layer was then extracted twice with diethyl ether (Et_2O) (10 mL) and once with AcOEt (10 mL). The combined organic layers were washed with an aqueous saturated Na_2SO_3 solution (20 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on silica gel.

4.5.1. 2-Bromofuro[3,2-b]pyridine (**5a**)

2-Bromofuro[3,2-*b*]pyridine **5a** was prepared according to the general method described herein with carbon tetrabromide (797 mg, 2.4 mmol, 2.0 equiv) as electrophile, for 1 h at −95 °C. Purification on silica gel was performed with hexane/AcOEt: 9:1 to 7:3 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **5a** (180 mg, 76%) as a white solid; mp 102–104 °C; ^{1}H NMR δ_H 6.98 (s, 1H, H_3), 7.20 (dd, J=8.3 Hz, J'=4.8 Hz, 1H, H_6), 7.71 (d, J=8.3 Hz, 1H, H_7), 8.51 (dd, J=4.8 Hz, J'=1.0 Hz, 1H, H_5); ^{13}C NMR δ_C 110.1 (C_3), 117.8 (C_6), 119.1 (C_7), 133.6 (C_2), 146.5 (C_5), 148.3 (C_{3a}), 154.5 (C_{7a}); IR (KBr) ν 1610, 1408, 1153; MS (CI) *m*/*z* 228 (16), 226 ([M+29]$^+$, 15), 200 (99), 198 ([M+1]$^+$, 100), 147 (16), 119 (11), 90 (16).

4.5.2. Furo[3,2-b]pyridin-2-ylphenylmethanol (**5b**)

Furo[3,2-*b*]pyridin-2-ylphenylmethanol **5b** was prepared according to the general method described herein with benzaldehyde (255 mg, 2.4 mmol, 2.0 equiv) as electrophile, for 1 h at −78 °C. Purification on silica gel was performed with hexane/AcOEt: 7:3 to 0:10 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **5b** (258 mg, 95%) as a brown solid; mp, ^{1}H, IR and MS are in conformity with the literature;[16] ^{13}C NMR δ_C 70.3 (*C*HOH), 104.3 (C_3), 118.4 (C_6), 118.7 (C_7), 126.9 (C_{Ar}), 128.3 (C_{Ar}), 128.6 (C_{Ar}), 140.5 (C_{Ar}), 145.1 (C_5), 147.8 (C_{3a}), 148.1 (C_{7a}), 164.2 (C_2).

4.5.3. 2-Methylsulfanylfuro[3,2-b]pyridine (**5c**)

2-Methylsulfanylfuro[3,2-*b*]pyridine **5c** was prepared according to the general method described herein with dimethyldisulfide (226 mg, 2.4 mmol, 2.0 equiv) as electrophile, for 1 h at −78 °C. Purification on silica gel was performed with hexane/AcOEt: 7:3 to 5:5 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **5c** (176 mg, 89%) as an orange solid; mp 38–40 °C; ^{1}H NMR δ_H 2.59 (s, 1H, CH_3), 6.79 (s, 1H, H_3), 7.13 (dd, J=8.3 Hz, J'=4.8 Hz, 1H, H_6), 7.64 (d, J=8.3 Hz, 1H, H_7), 8.46 (d, J=4.8 Hz, 1H, H_5); ^{13}C NMR δ_C 15.8 (*C*H$_3$), 106.4 (C_3), 116.9 (C_6), 118.0 (C_7), 145.6 (C_5), 148.5 (C_{3a}), 148.8 (C_{7a}), 158.4 (C_2); IR (KBr) ν 1610, 1411, 1260, 1158; MS (CI) *m*/*z* 194 ([M+29]$^+$, 16), 166 ([M+1]$^+$, 100).

4.5.4. 2-Trimethylsilanylfuro[3,2-b]pyridine (**5d**)

2-Trimethylsilanylfuro[3,2-*b*]pyridine **5d** was prepared according to the general method described herein with trimethysilyl chloride (260 mg, 2.4 mmol, 2.0 equiv) as electrophile, for 1 h at −78 °C. Purification on silica gel was performed with hexane/AcOEt: 9:1 to 7:3 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **5d** (160 mg, 70%) as a yellow oil. Spectroscopic data are in conformity with the literature.[28]

4.5.5. 2-Tri-n-butylstannanylfuro[3,2-b]pyridine (**5e**)

2-Tri-*n*-butylstannanylfuro[3,2-*b*]pyridine **5e** was prepared according to the general method described herein with chlorotri-*n*-butyltin (781 mg, 2.4 mmol, 2.0 equiv) as electrophile, for 15 min at −95 °C. Purification on silica gel was performed with hexane/AcOEt: 9:1 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **5e** (410 mg, 84%) as a colourless oil; ^{1}H NMR δ_H 0.90 (t, J=7.3 Hz, 9H, CH_3), 1.16–1.22 (m, 6H, CH_2), 1.32–1.39 (m, 6H, CH_2), 1.56–1.65 (m, 6H, CH_2), 7.12 (s, 1H, H_3), 7.13 (dd, J=8.3 Hz, J'=4.7 Hz, 1H, H_6), 7.73 (d, J=8.3 Hz, 1H, H_7), 8.49 (dd, J=4.7 Hz, J'=1.0 Hz, 1H, H_5); ^{13}C NMR δ_C 10.4 (Sn*C*H$_2$), 13.8 (*C*H$_3$), 27.3 (*C*H$_2$), 29.0 (*C*H$_2$), 117.6 (C_6), 117.9 (C_7), 119.5 (C_3), 145.2 (C_5), 148.5 (C_{3a}), 151.2 (C_{7a}), 171.7 (C_2); IR (NaCl) ν 2922, 1605, 1406, 1255, 1142; MS (CI) *m*/*z* 438 ([M+29]$^+$, 22), 410 ([M+1]$^+$, 93), 352 ([M−57]$^+$, 100), 291 (19), 235 (10).

4.5.6. Furo[3,2-b]pyridin-2-carbaldehyde (**5f**)

Furo[3,2-*b*]pyridin-2-carbaldehyde **5f** was prepared according to the general method described herein with dimethylformamide (175 mg, 2.4 mmol, 2.0 equiv) as electrophile, for 1 h at −78 °C. Purification on silica gel was performed with hexane/AcOEt: 7:3 to 5:5 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **5f** (150 mg, 85%) as a white solid. Spectroscopic data are in conformity with the literature.[24a,29]

4.6. Preparation of 2-substituted furo[3,2-*b*]pyridines (6–11) using a Pd-catalyzed cross-coupling

4.6.1. [2,2′]Bi[furo[3,2-b]pyridinyl] (**6**)

Under argon atmosphere, to a suspension of $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol, 5 mol %) in DMF (1.5 mL) were added 2-tri-*n*-butylstannanylfuro[3,2-*b*]pyridine **5e** (151 mg, 0.37 mmol, 1.1 equiv) and 2-bromofuro[3,2-*b*]pyridine **5a** (67 mg, 0.34 mmol, 1.0 equiv). After stirring at 110 °C for 2 h, the reaction medium was diluted in CH_2Cl_2 (20 mL) and washed with an aqueous saturated Na_2SO_3 solution (10 mL). After drying ($MgSO_4$) and solvent evaporation, the crude product was purified by column chromatography on silica gel (eluent: hexane/AcOEt 7:3 to 0:10) to afford the expected bisfuro[3,2-*b*]pyridinyl derivative **6** (74 mg, 92%) as a yellow powder; mp 214–217 °C; ^{1}H NMR δ_H 7.28 (dd, J=8.3 Hz, J'=4.7 Hz, 2H, H_6), 7.42 (s, 2H, H_3), 7.82 (d, J=8.3 Hz, 2H, H_7), 8.59 (d, J=4.7 Hz, 2H, H_5); ^{13}C NMR δ_C 105.8 (C_3), 118.3 (C_6), 120.0 (C_7), 147.0 (C_5), 147.8 (C_{3a}), 148.6 (C_{7a}), 150.2 (C_2); IR (KBr) ν 1607, 1414, 1275, 1167; MS (CI) *m*/*z* 265 ([M+29]$^+$, 22), 237 ([M+1]$^+$, 100); ESI-HRMS calcd for $C_{14}H_8N_2O_2$ (M+H)$^+$: 237.0659, found: 237.0670.

4.6.2. 2-Pyridin-3-ylfuro[3,2-b]pyridine (**7**)

2-Pyridin-3-ylfuro[3,2-*b*]pyridine **7** was prepared according to the method described herein for derivative **6**, using 3-bromopyridine (54 mg, 0.34 mmol, 1.0 equiv). Purification on silica gel was performed with hexane/AcOEt: 7:3 to 5:5 as eluent to afford the expected furo[3,2-*b*]pyridinyl derivative **7** (33 mg, 50%) as a white powder; mp 137–139 °C; ^{1}H NMR δ_H 7.23 (dd, J=8.3 Hz, J'=4.8 Hz, 1H, H_6), 7.30 (d, J=0.9 Hz, 1H, H_3), 7.40 (ddd, J=8.0 Hz, J'=4.8 Hz, J''=0.9 Hz, 1H, $H_{5'}$), 7.76–7.82 (m, 1H, H_7), 8.14 (ddd, J=8.0 Hz, J'=2.2 Hz, J''=1.7 Hz, 1H, $H_{4'}$), 8.55 (dd, J=4.8 Hz, J'=1.3 Hz, 1H, H_5), 8.63 (dd, J=4.8 Hz, J'=1.7 Hz, 1H, $H_{6''}$), 9.14 (d, J=2.2 Hz, 1H, $H_{2'}$); ^{13}C NMR δ_C 103.9 (C_3), 118.2 (C_6), 119.5 (C_7), 123.8 ($C_{5'}$), 125.9 ($C_{3'}$), 132.4 ($C_{4'}$), 146.6 (C_5), 146.8 ($C_{6'}$), 148.3 (C_{3a}), 148.6 (C_{7a}), 150.3 ($C_{2'}$), 156.7 (C_2); IR (KBr) ν 1607, 1406, 1252, 1161; MS (CI) *m*/*z* 225

([M+29]$^+$, 22), 197 ([M+1]$^+$, 100); ESI-HRMS calcd for $C_{12}H_8N_2O$ (M+H)$^+$: 197.0709, found: 197.0725.

4.6.3. 2-Pyridin-2-ylfuro[3,2-b]pyridine (**8**)

2-Pyridin-2-ylfuro[3,2-*b*]pyridine **8** was prepared according to the method described herein for derivative **6**, using 2-bromopyridine (54 mg, 0.34 mmol, 1.0 equiv). Purification on silica gel was performed with hexane/AcOEt: 7:3 to 5:5 as eluent to afford the expected furo[3,2-*b*]pyridinyl derivative **8** (41 mg, 62%) as a white powder; mp 111–113 °C; ^{1}H NMR δ_H 7.23–7.35 (m, 2H, H_6,$H_{5'}$), 7.62 (s, 1H, H_3), 7.78–7.87 (m, 2H, H_7, $H_{3'}$), 7.95 (d, J=7.9 Hz, 1H, $H_{4'}$), 8.58 (dd, J=4.7 Hz, J'=1.2 Hz, 1H, H_5), 8.73 (d, J=4.8 Hz, $H_{6'}$); ^{13}C NMR δ_C 105.9 (C_3), 118.5 (C_6), 119.8 (C_7), 120.4 ($C_{5'}$), 123.9 ($C_{3'}$), 137.0 ($C_{4'}$), 146.7 (C_5), 147.1 (C_{3a}), 148.6 (C_{7a}), 148.6 ($C_{2'}$), 150.3 ($C_{6'}$), 158.5 (C_2); IR (KBr) ν 1610, 1414, 1260, 1167; MS (CI) m/z 225 ([M+29]$^+$, 22), 197 ([M+1]$^+$, 100); ESI-HRMS calcd for $C_{12}H_8N_2O$ (M+H)$^+$: 197.0709, found: 197.0739.

4.6.4. 2-Trimethylsilanylethynylfuro[3,2-b]pyridine (**9**)

Under argon atmosphere, to a suspension $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol, 5 mol %) and CuI (10 mg, 0.05 mmol, 10 mol %) in THF (2 mL), in the presence of Et_3N (1.5 mL, 7.5 mmol, 15.0 equiv) were added in one portion 2-bromofuro[3,2-*b*]pyridine **5a** (99.0 mg, 0.5 mmol, 1.0 equiv) and trimethylsilylacetylene (64 mg, 0.65 mmol, 1.3 equiv) in THF (2 mL). After stirring at room temperature for 12 h, the reaction mixture was diluted in AcOEt (20 mL) and washed with an aqueous saturated Na_2SO_3 solution (10 mL). After drying ($MgSO_4$) and solvent evaporation, the crude product was purified by column chromatography on silica gel (eluent: hexane/AcOEt 9:1 to 7:3) to afford the expected furo[3,2-*b*]pyridinyl derivative **9** (93.0 mg, 87%) as a brown powder; mp 44–46 °C; ^{1}H NMR δ_H 0.31 (s, 9H, SiCH_3), 7.15 (s, 1H, H_3), 7.26 (dd, J=8.4 Hz, J'=4.7 Hz, 1H, H_6), 7.70 (d, J=8.4 Hz, 1H, H_7), 8.57 (dd, J=4.7 Hz, 1H, H_5); ^{13}C NMR δ_C −0.4 (CH_3Si), 93.6 (C), 104.3 (C), 112.8 (C_3), 118.2 (C_6), 120.2 (C_7), 142.2 (C_2), 146.9 (C_5), 147.3 (C_{3a}), 148.1 (C_{7a}); IR (KBr) ν 2156, 1406, 1250, 1167; MS (CI) m/z 244 ([M+29]$^+$, 22), 216 ([M+1]$^+$, 100), 200 (22); ESI-HRMS calcd for $C_{12}H_{13}NOSi$ (M+H)$^+$: 216.0839, found: 216.0858.

4.6.5. 2-Vinylfuro[3,2-b]pyridine (**10**)

Under argon atmosphere, to a suspension of $PdCl_2(PPh_3)_2$ (88 mg, 0.125 mmol, 5 mol %) in DMF (10 mL) were added 2-bromofuro[3,2-*b*]pyridine **5a** (495.0 mg, 2.5 mmol, 1.0 equiv) and vinyltributyltin (872 mg, 2.75 mmol, 1.1 equiv). After stirring at 110 °C for 2 h, the reaction mixture was diluted in CH_2Cl_2 (20 mL), washed with an aqueous saturated Na_2SO_3 solution (10 mL) and dried ($MgSO_4$). After solvent evaporation, column chromatography purification on silica gel was performed with hexane/AcOEt: 9:1 to 7:3 as eluent to afford the expected furo[3,2-*b*]pyridinyl derivative **10** (300.0 mg, 83%) as a brown oil; ^{1}H NMR δ_H 5.49 (dd, J=11.5 Hz, J'=0.8 Hz, 1H, CH_2), 6.06 (dd, J=17.7 Hz, J'=0.8 Hz, 1H, CH_2), 6.69 (dd, J=17.7 Hz, J'=11.5 Hz, 1H, CH), 6.81 (s, 1H, H_3), 7.18 (dd, J=8.3 Hz, J'=4.8 Hz, 1H, H_6), 7.69 (d, J=8.3 Hz, 1H, H_7), 8.48 (dd, J=4.8 Hz, J'=1.2 Hz, 1H, H_5); ^{13}C NMR δ_C 105.7 (C_3), 117.8 (CH$_2$), 117.9 (C_6), 119.2 (C_7), 125.2 (CH), 146.0 (C_5), 148.0 (C_{3a}), 148.7 (C_{7a}), 158.3 (C_2); IR (NaCl) ν 1414, 1263, 1159; MS (CI) m/z 174 ([M+29]$^+$, 22), 146 ([M+1]$^+$, 100).

4.6.6. 2-Furo[3,2-b]pyridin-2-yl-benzaldehyde (**11**)

Under argon atmosphere, to a suspension of $Pd(PPh_3)_4$ (289.0 mg, 0.25 mmol, 5 mol %) in THF (20 mL) were added 2-bromofuro[3,2-*b*]pyridine **5a** (1.0 g, 5.05 mmol, 1.0 equiv), 2-formylbenzeneboronic acid (984.0 mg, 6.56 mmol, 1.3 equiv) and a 2 M Na_2CO_3 aqueous solution (5.05 mL, 10.10 mmol, 2.0 equiv). After stirring at reflux for 3 h, the reaction mixture was washed with H_2O (2×20 mL) and extracted with AcOEt (3×20 mL). Then, the combined organic layers were washed with a Na_2SO_3 saturated aqueous solution (30 mL) and dried ($MgSO_4$). After solvent evaporation, column chromatography purification on silica gel was performed with hexane/AcOEt: 7:3 to 5:5 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **11** (1.03 g, 91%) as a yellow powder; mp 112–114 °C; ^{1}H NMR δ_H 7.23 (s, 1H, H_3), 7.30 (dd, J=8.6 Hz, J'=5.0 Hz, 1H, H_6), 7.56–7.65 (m, 1H, H_{Ar}), 7.69–7.77 (m, 1H, H_{Ar}), 7.81–7.89 (m, 2H, H_{Ar}), 8.08 (dd, J=7.8 Hz, J'=1.3 Hz, 1H, H_7), 8.62 (dd, J=4.8 Hz, J'=1.3 Hz, 1H, H_5), 10.5 (s, 1H, CHO); ^{13}C NMR δ_C 108.8 (C_3), 118.5 (C_6), 119.8 (C_7), 128.6 (C_{Ar}), 129.7 (C_{Ar}), 130.1 (C_{Ar}), 132.4 (C_{Ar}), 133.9 (C_{Ar}), 134.2 (C_{Ar}), 146.8 (C_5), 148.3 (C_{3a}), 148.8 (C_{7a}), 157.0 (C_2), 191.6 (C=O); IR (KBr) ν 1691, 1414, 1268, 1193; MS (CI) m/z 252 ([M+29]$^+$, 15), 224 ([M+1]$^+$, 100), 195 (8); ESI-HRMS calcd for $C_{14}H_9NO_2$ (M+H)$^+$: 224.0706, found: 224.0731.

4.7. 2-Thiophen-2-ylfuro[3,2-b]pyridine (13)

To a solution of furo[3,2-*b*]pyridine **1** (143 mg, 1.2 mmol, 1.0 equiv) in THF (15 mL), at −78 °C, was added dropwise *n*-BuLi (1.5 mL, 2.4 mmol, 2.0 equiv) under argon atmosphere. After stirring for 1 h at −78 °C, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (446 mg, 2.4 mmol, 2.0 equiv) was added in THF (5 mL) at −78 °C. After stirring for 1 h at −78 °C, hydrolysis was performed using only few drops of water, the solvents were then evaporated. After flushing the medium with argon, a mixture of $Pd(PPh_3)_4$ (70.0 mg, 0.06 mmol, 5 mol %), 2-bromothiophene (215 mg, 1.32 mmol, 1.1 equiv) and a 2 M Na_2CO_3 aqueous solution (3.0 mL, 6.00 mmol, 2.0 equiv) in THF/toluene (1:1) (5 mL) was added. After stirring at reflux for 18 h, the reaction mixture was washed with H_2O (2×20 mL) and extracted with AcOEt (3×20 mL). The combined organic layers were washed with a Na_2SO_3 saturated aqueous solution (30 mL) and dried ($MgSO_4$). After solvent evaporation, a column chromatography purification on silica gel was performed with hexane/AcOEt: 9:1 to 5:5 as eluent and led to the expected furo[3,2-*b*]pyridinyl derivative **13** (89.0 mg, 37%) as a yellow powder; mp 74–76 °C; ^{1}H NMR δ_H 7.07 (s, 1H, H_3), 7.13–7.24 (m, 2H, H_6, H_{Ar}), 7.44 (dd, J=5.0 Hz, J'=1.1 Hz, 1H, H_{Ar}), 7.59 (dd, J=3.7 Hz, J'=1.1 Hz, 1H, H_{Ar}), 7.75 (d, J=8.2 Hz, 1H, H_7), 8.52 (dd, J=4.8 Hz, 1H, H_5); ^{13}C NMR δ_C 102.1 (C_3), 117.8 (C_6), 118.9 (C_7), 126.0 (C_{Ar}), 128.3 (C_{Ar}), 132.6 (C_{Ar}), 146.3 (C_5), 147.8 (C_{3a}), 149.1 (C_{7a}), 155.1 (C_2); IR (KBr) ν 1610, 1403, 1250, 1156; MS (EI) m/z 201 ([M]$^+$, 100), 172 (9), 108 (9); ESI-HRMS calcd for $C_{11}H_7NOS$ (M+H)$^+$: 202.0321, found: 202.0336.

4.8. 6,7,8,9-Tetrahydrobenzo[4,5]furo[3,2-b]pyridine-8,9-dicarboxylic acid diethyl ester (15)

To a solution of 2-vinylfuro[3,2-*b*]pyridine **10** (100.0 mg, 0.69 mmol, 1.0 equiv) in xylene (3 mL) was added fumarate diethyl ester (237.0 mg, 1.38 mmol, 2.0 equiv). The mixture was then refluxed for 48 h in a sealed tube. After a quick filtration and evaporation of solvents, a column chromatography purification on silica gel was performed with hexane/AcOEt: 7:3 to 5:5 as eluent and led to the expected derivative **15** (109 mg, 50%) as a yellow oil; ^{1}H NMR δ_H 1.19–1.34 (m, 6H, CH_3), 2.29–2.35 and 2.48–2.52 (2m, 2H, CH_2), 2.84–2.96 (m, 2H, CH_2), 3.30–3.35 (m, 1H, CHCH$_2$), 4.11–4.19 (m, 2H, CH_2CH$_3$), 4.20–4.28 (m, 2H, CH_2CH$_3$), 4.43 and 4.55 (2d, J=5.1 Hz, 1H, CH), 7.11–7.18 (m, 1H, H_3), 7.63–7.67 (m, 1H, H_4), 8.48 and 8.52 (2dd, J=4.7 Hz, J'=0.7 Hz, 1H, H_2); ^{13}C NMR δ_C 14.1 and 14.2 (CH_3), 21.0 and 21.8 (CH_2), 23.1 and 23.2 (CH_2), 38.6 and 40.0 (CH), 42.1 and 42.2 (CH), 61.0 and 61.2 (CH_2CH_3), 61.3 and 61.5 (CH_2CH_3), 117.6 and 117.7 (C_3), 118.2 and 118.3 (C_4), 145.4 and 145.5 (C_2), 147.1 (C_{9b}), 147.7 (C_{4a}), 158.6 (C_{9a}), 159.5 (C_{5a}), 172.5 (C=O), 172.7 (C=O); IR (NaCl) ν 1731, 1250; MS (EI) m/z 317 ([M]$^+$, 19), 244 (100), 198 (28), 170 (63); ESI-HRMS calcd for $C_{17}H_{19}NO_5$ (M+H)$^+$: 318.1336, found: 318.1321.

4.9. 3-Bromofuro[3,2-*b*]pyridine (5ab)

Spectroscopic data are in conformity with the literature.[23,29]

4.10. 2,3-Dibromofuro[3,2-*b*]pyridine (5ac)

Yellow solid; mp, ^{1}H NMR, and IR data are in conformity with the literature;[22e] ^{13}C NMR δ_C 102.0 (C_3), 118.6 (C_6), 120.4 (C_7), 133.9 (C_2), 145.7 (C_{3a}), 147.4 (C_5), 148.6 (C_{7a}); MS (EI) m/z 277 ([M]$^+$, 100), 168 (63).

4.11. 2,3,7-Tribromofuro[3,2-*b*]pyridine (5ad)

Yellow solid; mp 130–132 °C; ^{1}H NMR δ_H 7.48 (d, J=5.2 Hz, 1H, H_6), 8.41 (d, J=5.2 Hz, 1H, H_5); ^{13}C NMR δ_C 102.6 (C_3), 114.1 (C_7), 123.9 (C_6), 134.8 (C_2), 146.2 (C_{3a}), 147.0 (C_{7a}), 147.7 (C_5); MS (EI) m/z 355 ([M−1]$^+$, 100), 248 (70).

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References and notes

1. See for examples: (a) Comoy, C.; Marot, C.; Podona, T.; Baudin, M. L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D.-H.; Renard, P.; Rettori, M.-C.; Adam, G.; Guardiola-Lemaitre, B. *J. Med. Chem.* **1996**, *39*, 4285–4298; (b) Sebille, S.; Gall, D.; De Tullio, P.; Florence, X.; Lebrun, P.; Pirotte, B. *J. Med. Chem.* **2006**, *49*, 4690–4697; (c) Vasselin, D. A.; Westwell, A. D.; Matthews, C. S.; Bradshaw, T. D.; Stevens, M. F. G. *J. Med. Chem.* **2006**, *49*, 3973–3981.
2. See for examples: (a) Moreau, P.; Anizon, F.; Sancelme, M.; Prudhomme, M.; Bailly, C.; Carrasco, C.; Ollier, M.; Sevère, D.; Riou, J.-F.; Fabbro, D.; Meyer, T.; Aubertin, A.-M. *J. Med. Chem.* **1998**, *41*, 1631–1640; (b) Bromidge, S. M.; Dabbs, S.; Davies, D. T.; Duckworth, D. M.; Forbes, I. T.; Ham, P.; Jones, G. E.; King, F. D.; Saunders, D. V.; Starr, S.; Thewlis, K. M.; Wyman, P. A.; Blaney, F. E.; Naylor, C. B.; Bailey, F.; Blackburn, T. P.; Holland, V.; Kennett, G. A.; Riley, G. J.; Wood, M. D. *J. Med. Chem.* **1998**, *41*, 1598–1612; (c) Smid, P.; Coolen, H. K. A. C.; Keizer, H. G.; Van Hes, R.; De Moes, J.-P.; Den Hartog, A. P.; Stork, B.; Plekkenpol, R. H.; Niemann, L. C.; Stroomer, C. N. J.; Tulp, M. T. M.; Van Stuivenberg, H. H.; McCreary, A. C.; Hesselink, M. B.; Herremans, A. H. J.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 6855–6889; (d) Quintanar-Audelo, M.; Fernandez-Carvajal, A.; Van Den Nest, W.; Carreno, C.; Ferrer-Montiel, A.; Albericio, F. *J. Med. Chem.* **2007**, *50*, 6133–6143.
3. (a) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031–1064 and references cited herein; (b) Popowycz, F.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689–8707 and references cited herein.
4. Comoy, C.; Banaszak, E.; Fort, Y. *Tetrahedron* **2006**, *62*, 6036–6041.
5. Banaszak, E.; Comoy, C.; Fort, Y. *Tetrahedron Lett.* **2006**, *47*, 6235–6238.
6. Comoy, C.; Pétrignet, J.; Banaszak, E.; Chartoire, A.; Fort, Y., submitted for publication.
7. Gronowitz, S.; Westerlund, C.; Hörnfeldt, A.-B. *Acta Chem. Scand., Ser. B* **1975**, *29*, 233–238.
8. Hickson, C. L.; McNab, H. *Synthesis* **1981**, 464–465.
9. Shiotani, S.; Morita, H. *J. Heterocycl. Chem.* **1986**, *23*, 665–668.
10. Shiotani, S. *Heterocycles* **1997**, *45*, 975–1011.
11. Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791–2793.
12. Campos, P. J.; Anon, E.; Malo, M. C.; Rodriguez, M. A. *Tetrahedron* **1999**, *55*, 14079–14088.
13. Kitamura, T.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, *39*, 5375–5376.
14. Mathes, B. M.; Filla, S. A. *Tetrahedron Lett.* **2003**, *44*, 725–728.
15. For example see: (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271; (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690; (c) Larock, R. C.; Yum, E. R.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662; (d) Bishop, B. C.; Cottrell, I. F.; Hands, D. *Synthesis* **1997**, 1315–1320; (e) Zhang, H.-C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439–2442; (f) Zhang, H.-C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751–4754; (g) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355–5358; (h) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S. *Tetrahedron Lett.* **1993**, *34*, 2823–2826; (i) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S. *Tetrahedron Lett.* **1993**, *34*, 6471–6474.
16. Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, *9*, 749–751.
17. Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292–10296.
18. Arcadi, A.; Cacchi, S.; Di Guiseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409–2412.
19. Arcadi, A.; Cacchi, S.; Di Guiseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453–457.
20. Lindstrom, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291–2293.
21. Crude **3**, obtained after a simple filtration on silica gel column, was used in preparative experiments without decrease of **1** isolated yields.
22. (a) Shiotani, S.; Taniguchi, K. *J. Heterocycl. Chem.* **1996**, *33*, 1051–1056; (b) Shiotani, S.; Tsukamoto, Y. *J. Heterocycl. Chem.* **1997**, *34*, 129–141; (c) Shiotani, S.; Tanigochi, K. *J. Heterocycl. Chem.* **1997**, *34*, 901–929; (d) Yamaguchi, S.; Kurosaki, M.; Orito, K.; Yokayama, H.; Hirai, Y.; Shiotani, S. *J. Heterocycl. Chem.* **1998**, *35*, 1237–1247; (e) Yamaguchi, S.; Awajima, K.; Hirai, Y.; Yokoyama, H.; Shiotani, S. *J. Heterocycl. Chem.* **1998**, *35*, 1249–1255.
23. Shiotani, S.; Morita, H.; Inoue, M.; Ishida, T.; Iitaka, Y.; Itai, A. *J. Heterocycl. Chem.* **1984**, *21*, 725–736.
24. (a) Morita, H.; Shiotani, S. *J. Heterocycl. Chem.* **1987**, *24*, 373–376; (b) Shiotani, S.; Morita, H. *J. Heterocycl. Chem.* **1992**, *29*, 413–422.
25. Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375–3383.
26. See for example: Plé, N.; Turck, A.; Chapoulaud, V.; Quéguiner, G. *Tetrahedron* **1997**, *53*, 2871–2890.
27. Le Strat, F.; Vallette, H.; Toupet, L.; Maddaluno, J. *Eur. J. Org. Chem.* **2005**, 5296–5305.
28. Park, S. K.; Baek, D. J. *J. Photochem. Photobiol., A* **2003**, *157*, 15–22.
29. Shiotani, S.; Morita, H. *J. Heterocycl. Chem.* **1991**, *28*, 1469–1480.