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Charting the chemical reactivity space of 2,3-substituted furo[2,3-*b*]pyridines synthesized via the heterocyclization of pyridine-*N*-oxide derivatives

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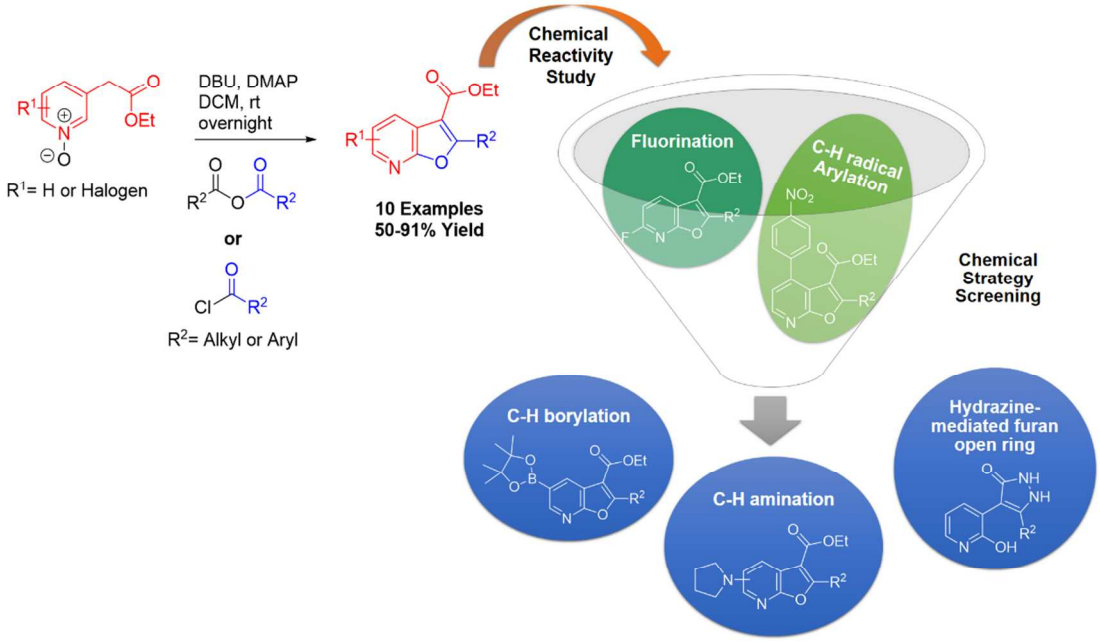
GRAPHICAL ABSTRACT



ABSTRACT: A concise strategy for the synthesis of 2,3-substituted furo[2,3-*b*]pyridines is described. Mild, metal-free conditions were successfully applied to produce a range of 2-(alkyl or aryl)-3-ethylcarboxylate-furo[2,3-*b*]pyridines in yields of 50-91%. Then, the chemical reactivity of this heterocyclic framework was explored to develop straightforward methods for its functionalization. The pyridine moiety reactivity was successfully explored by

C–H amination and borylation reactions, although C–H fluorination and radical C–H arylation processes were not as efficient. In addition, while the furopyridine core proved stable under basic conditions, the ring-opening reaction of the furan moiety with hydrazine generated a valuable new pyridine-dihydropyrazolone scaffold.

INTRODUCTION

The furo[2,3-*b*]pyridine core has recently received extensive attention from the medicinal chemistry community as a useful pharmacophore for the development of several drug candidates in different therapeutic areas (Figure 1).[1] This heterocyclic core can be found in the structure of **1**, a highly active type 1 cannabinoid receptor (CB1R) modulator, active in the treatment of food-borne diseases.[2] It is also found in compound **2**, a protein kinase inhibitor and candidate for cancer treatment.[3] Pharmacological studies of compound **3** and its derivatives, designed from the structure of the antiviral Nesbuvir, have demonstrated their high activity against the hepatitis C virus by the inhibition of nonstructural protein 5B (NS5B).[4]

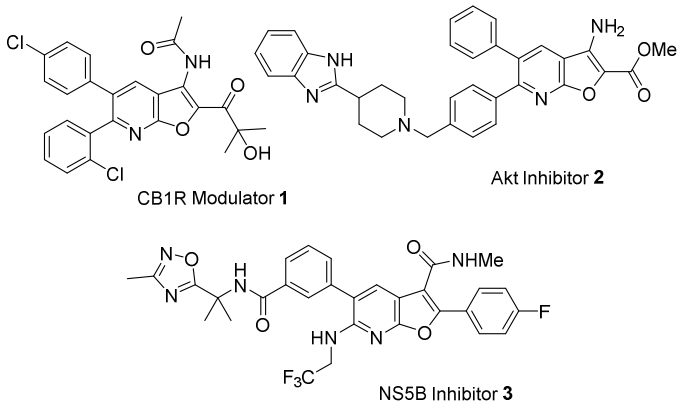
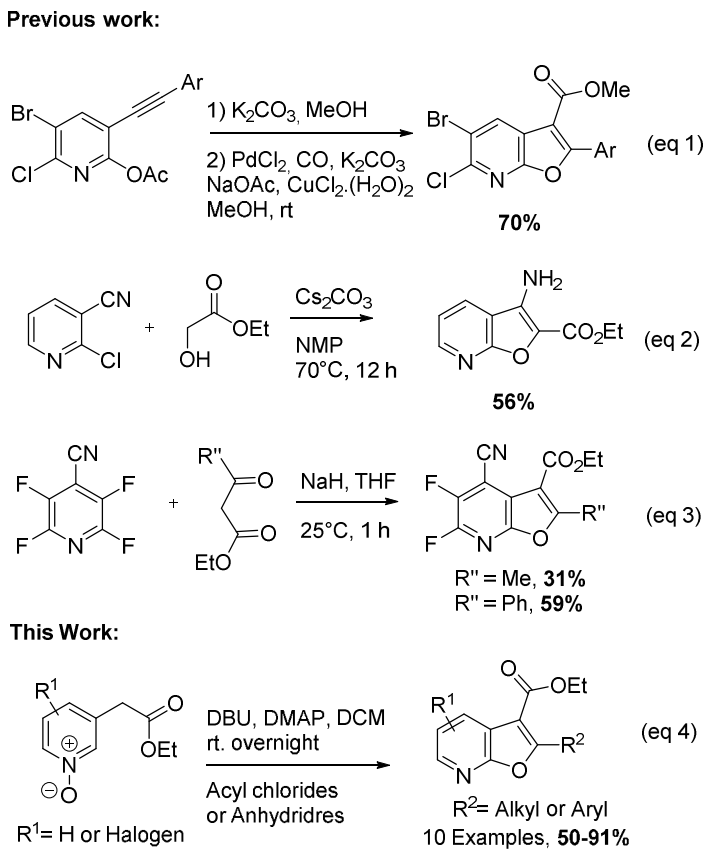


Figure 1. Representative examples of biologically active furo[2,3-*b*]pyridine derivatives.

Despite their importance, synthetic methodologies for furopyridines remain limited.[5] There are two main strategies for the synthesis of this heterocyclic fragment, differing by the

heterocyclic starting material, whether furan or pyridine.[6] To the best of our knowledge, when pyridine substrates are used, only three methods to obtain furo[2,3-*b*]pyridine 2,3-substituted compounds (Scheme 1) have been described in the literature. Eastman *et al*.[4] explored the Sonogashira coupling, producing 2-hydroxy-3-alkyne-substituted pyridines that underwent palladium-catalyzed cyclization to afford the furan ring (eq 1). Cailly *et al*.[7] used nucleophilic aromatic substitution to synthesize a 3-amino-furo[2,3-*b*]pyridine-2-carboxylate (eq 2), and Cartwright *et al*.[8] reported furopyridine core construction by the annelation of perfluorinated pyridines using 1,3-dicarbonyl derivatives (eq 3).

Scheme 1. Synthetic strategies for 2,3-substituted furo[2,3-*b*]pyridine derivatives



In addition to the lack of synthetic strategies for this heteroaromatic core, descriptions of its reactivity, especially of the pyridine ring, are limited.[1,9] For example, the pyridine ring of furo[2,3-*b*]pyridines was found to be reactive to electrophiles and nucleophiles when oxidized to the *N*-oxide derivative: cyanation and acetoxylation typically occur at C-6, whereas chlorination proceeds at C-4.[10,11] Therefore, the chemical reactivity of the pyridine moiety remains synthetically underexplored, as is the development of more efficient strategies for generating the furopyridine core.

In this work, we describe a facile and concise strategy for the synthesis of 2,3-substituted furo[2,3-*b*]pyridines from pyridine-*N*-oxide derivatives (eq 4). Under mild, metal-free conditions, we synthesized ten examples by the reaction of the pyridine-*N*-oxides with acyl chlorides or anhydrides in yields up to 91%. In addition, considering the recent advances in the C–H activation of electron-deficient rings,[12] we explored the reactivity of this heteroaromatic core through C–H amination,[13] radical C–H arylation,[14] and C–H fluorination[15] reactions, as well as in a C–H borylation/Suzuki coupling reaction sequence.[16] Finally, the reactivity of the furan moiety in the presence of nucleophiles was evaluated, as well as its stability under basic conditions.

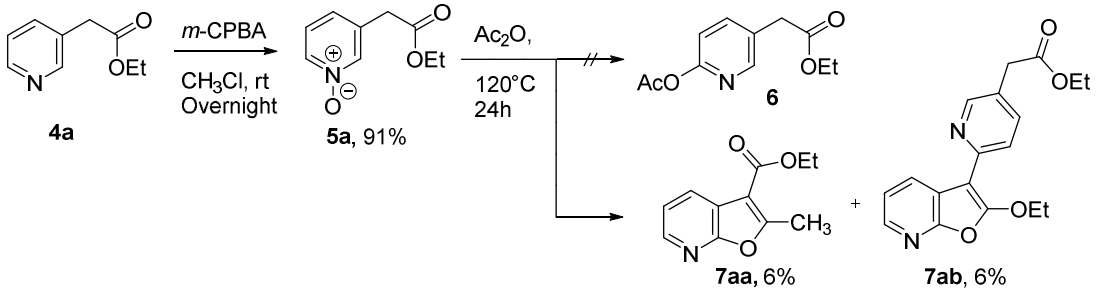
RESULTS AND DISCUSSION

Development of synthetic strategy for 2,3-substituted furo[2,3-*b*]pyridines

While attempting to produce 2-acetoxypyridine **6** from the reaction of *N*-oxide **5a** with acetic anhydride (Scheme 2), the fully characterized furo[2,3-*b*]pyridines **7aa** and **7ab** were instead observed in low conversion and yield. This unexpected result spurred us to study the reaction, both to improve the yield and selectivity of **7aa** and possibly develop a more efficient,

alternative synthesis of reaction intermediates used to obtain antiviral compound **3** (Figure 1).[4]

Scheme 2. Synthesis of furo[2,3-*b*]pyridine derivatives from pyridine 4a.



A plausible mechanism for the formation of these furopyridines, supported by the optimization study, is presented in Scheme 3. In both cases, the *N*-acetoxypyridine derivative is formed (**A**), which is subsequently deprotonated at the benzylic position to form an enolate (**B**). For **7aa**, the enolate reacts with another equivalent of anhydride to afford an ethyl acetoacetate derivative (**C**), whereas for **7ab**, the enolate reacts with a second *N*-acetoxypyridine derivative (**F**). In the next step, the hydrogen alpha to the carbonyl group is deprotonated and heterocyclization occurs (**D** and **G**). Finally, furopyridines **7aa** and **7ab** are formed after deprotonation and re-aromatization processes (**E** and **H**).

Scheme 3. **Proposed reaction mechanism for the synthesis of 7aa and 7ab.**

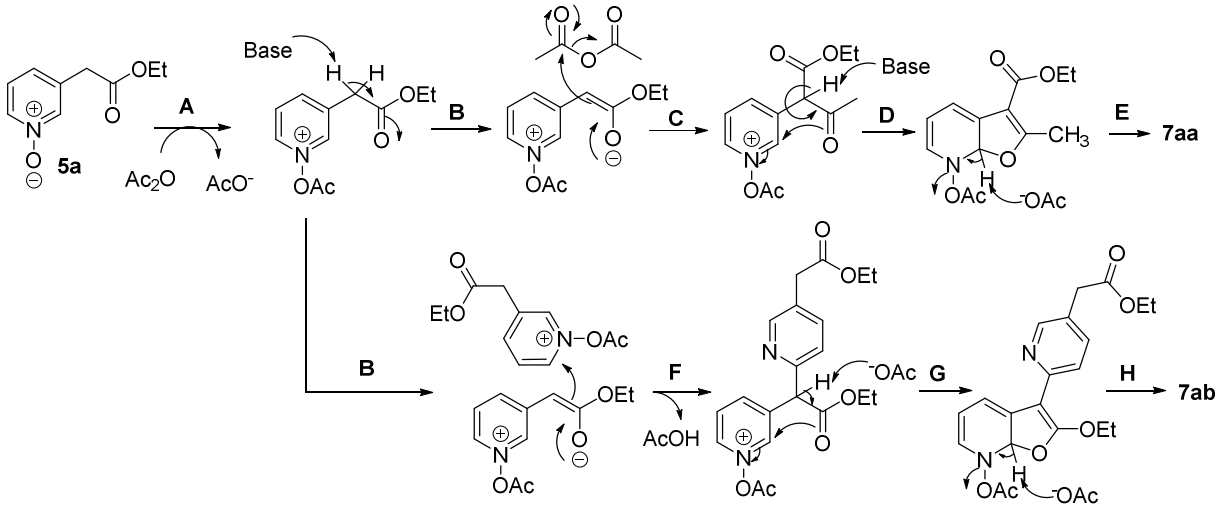
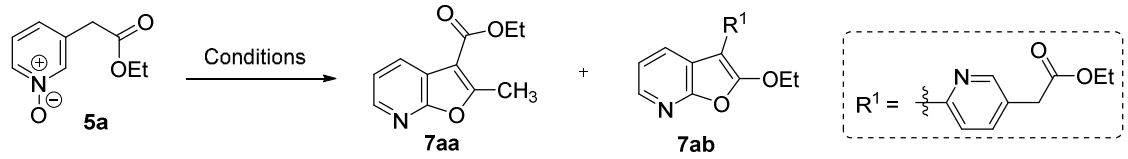


Table 1. Optimization of reaction conditions for the synthesis of 2,3-substituted furo[2,3-*b*]pyridines



Entry	Solvent	Acyl Source	DMAP	Base (1.2 equiv)	Temp	Yield [%][a] (ratio 7aa/7ab)
1	Ac_2O	Ac_2O	-	-	120°C	12 (1:1)
2	Ac_2O	Ac_2O	-	*t*BuONa	120°C	20 (1:1)
3	Ac_2O	Ac_2O	-	DBU	120°C	45 (8:2)
4	Ac_2O	Ac_2O	-	DBU	rt	10 (1:0)
5	Ac_2O	Ac_2O	2 equiv	-	rt	75 (1:0)
6	Ac_2O	Ac_2O	2 equiv	DBU	rt	83 (1:0)
7	DCM	Ac_2O (4 equiv)	4 equiv	DBU	rt	60 (1:0)
8	DCM	Ac_2O (6 equiv)	6 equiv	DBU	rt	80 (1:0)
9	DCM	Ac_2O (6 equiv)	2 equiv	DBU	rt	78 (1:0)
10	DCM	Ac_2O (6 equiv)	1 equiv	DBU	rt	70 (1:0)
11	DCM	Ac_2O (6 equiv)	0.1 equiv	DBU	rt	60 (1:0)
12	DCM	Ac_2O (6 equiv)	2 equiv	DBU[b]	rt	70 (1:0)
13	DCM	CH_3COCl (4 equiv)	4 equiv	DBU	rt	06 (1:0)
14	DCM	CH_3COCl (6 equiv)	6 equiv	DBU	rt	50 (1:0)
15	DCM	CH_3COCl (6 equiv)	2 equiv	DBU	rt	05 (1:0)

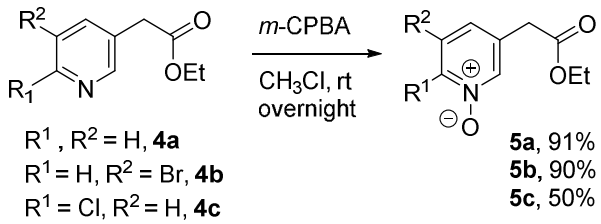
[a]Yield of isolated product after overnight reaction.[b]Reaction carried out with 0.1 equiv of DBU.

Considering the assistance by acetate for heterocyclization, according to the mechanism proposed, we initially studied the influence of an additional source of base in the reaction (Table 1, Entries 2 and 3). The acetate formed under the original conditions was not a sufficiently strong base to efficiently perform the reaction. To our delight, DBU proved to be

a good choice (Table 1, Entry 3), improving the yield (45%) and selectivity for **7aa** over **7ab** (8:2). Selectivity for **7aa** was improved at lower temperature in the presence of DBU, albeit in low yield (Table 1, Entry 4). The addition of DMAP increased the electrophilicity of the acetylating reagent, resulting in higher heterocyclization yields (Table 1, Entries 5 and 6). This suggests that the initial acetylation step is rate-limiting, because heterocyclization was poor even when using a large excess of acetic anhydride. Interestingly, the use of acetyl chloride as the acetylating reagent reduced the yield when compared to Ac_2O, even in the presence of DMAP (Table 1, Entries 6 to 15). It was found that, when acetic anhydride is used in excess (6 equiv), just 2 equiv DMAP are necessary to selectively produce furopyridine **7aa** in good yield (Table 1, Entry 9), although for acyl chlorides, 6 equiv DMAP are required (Table 1, Entry 14). In addition, the use of catalytic amounts of DBU and DMAP (Table 1, Entries 11 and 12) did not reduce the yields to a great extent. Based on these results, we determined that the heterocylization of pyridine-*N*-oxides with acyl anhydrides or chlorides proceeded optimally in the presence of DBU and DMAP, using DCM as solvent (Table 1, Entries 9 and 14, respectively). These conditions were applied while evaluating the scope of reaction, as described below.

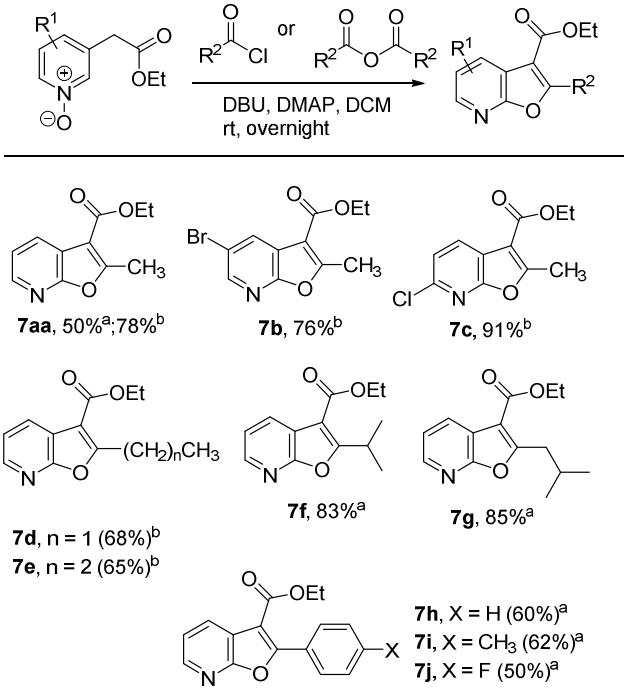
After optimizing the reaction and understanding the probable mechanism, we evaluated the substrate scope. First, the starting substrates were synthesized (Scheme 4). Halogenated compounds **4b** and **4c** were obtained from their respective commercially available acids. Pyridine-*N*-oxide derivatives **5a–c** were synthesized in yields comparable to those reported in the literature.[17–19]

Scheme 4. Synthesis of pyridine-*N*-oxide derivatives



Using the optimized methods for anhydrides and acyl chlorides, ten new 2-(alkyl or aryl)-3-ethylcarboxylate-furo[2,3-*b*]pyridine compounds were obtained in good to excellent yields (Scheme 5). The 2-alkyl-substituted furopyridines were obtained in better yields compared to aryl-substituted ones. The use of trifluoroacetic anhydride, chloroformates, or cyclic anhydrides did not afford the desired furo[2,3-*b*]pyridines. According to these results, we established that our methodology could be applied successfully with both alkyl and aryl anhydrides or acyl chlorides, as well as substituted pyridines, and thus produce a diverse library of furo[2,3-*b*]pyridines.

Scheme 5. Scope of reaction for the synthesis of 2,3-substituted furo[2,3-*b*]pyridines



Reaction conditions: Pyridine-*N*-oxide (1.0 equiv), acyl source (6 equiv), DBU (1.2 equiv), DMAP (6 equiv[a] or 2

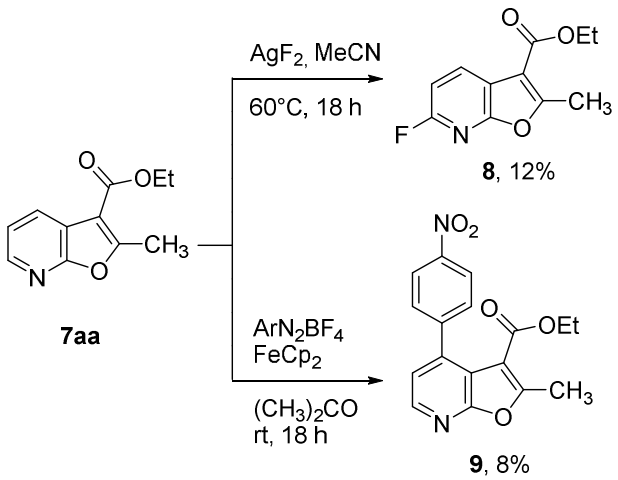
equiv[b]), DCM, room temperature, overnight. [a]Reaction performed with acyl chlorides. [b]Reaction performed with anhydrides.

Chemical reactivity of the pyridine moiety of the furo[2,3-*b*]pyridine core

We explored the chemical tractability of the furopyridine core, in order to understand the reactivity of the electron-poor ring and provide strategies for chemical library development. Although there have recently been advances in the C–H activation of electron-deficient rings,[12] this subject remains a challenge for synthetic chemists, considering the large amount of heteroaryl substrates necessary to carry out the reaction.[20] Herein, we applied some of the most efficient reported strategies for these cases to substrate **7aa**.

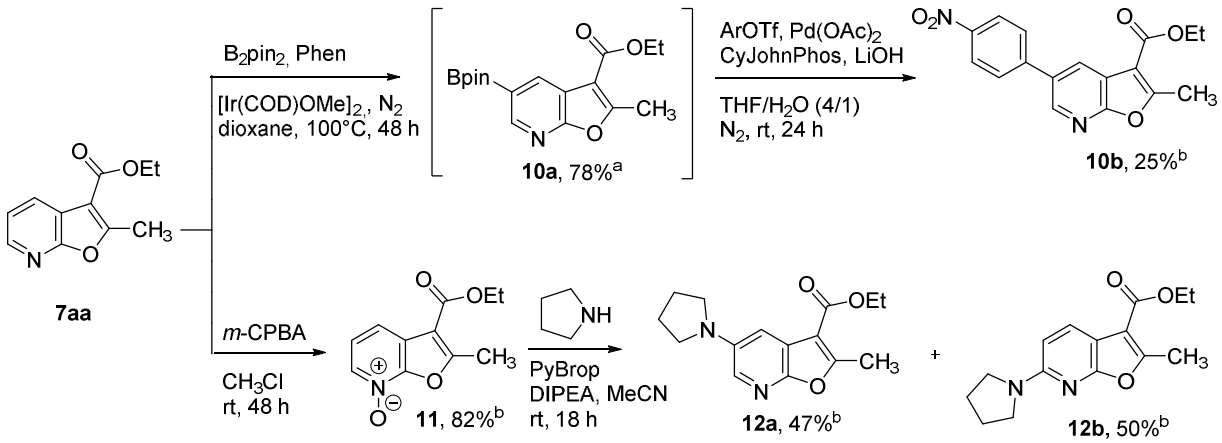
Preliminary studies involving C–H fluorination[15] and radical C–H arylation with aryldiazonium salts[14] were unsuccessful, furnishing the desired products in low yields (Scheme 6), with substitutions in C-6 and C-4, respectively. In both cases, the isolated products reflect typically observed pyridine reactivity, with α and γ substitution for fluorination and arylation, respectively.[14,15] These results illustrates the challenge mentioned before. The direct fluorination of electron-poor heteroarenes is an incipient chemistry field, with just few successful examples and some limitations reported.[15,21] Same reactivity is described for the radical arylation of π-deficient heterocycles, which in some case are known to have low yields, with better results when large excess of the heterocyclic ring are used.[22]

Scheme 6. C–H fluorination and radical C–H arylation of furo[2,3-*b*]pyridine core



Although limited results were observed for these previous showed reactions, with slightly lower yields compared to similar systems in the literature, the findings were enough stimulation in challenging us to find efficient ways to decorate the furo[2,3-*b*]pyridine. Recently, the Hartwig group reported the efficient iridium-catalyzed C−H borylation of azaindoles, yielding unstable boronic esters that were used in Suzuki cross-coupling reactions.[16] In our studies, Hartwig's C–H borylation method was efficient in converting the starting material, furnishing a product which proved to be unstable during purification by column chromatography. Monitoring the reaction by GC-MS, the site-selective process yielded 78% of boronate furopyridine **10a**, which was directly used as a substrate in the Suzuki coupling reaction in a tandem procedure (Scheme 7), using optimal known conditions for these type of substrates.[23] Although the isolated yield for arylation was poor (**10b**, 25%), the structure elucidation confirmed the *β*-functionalization, following the same reactivity pattern as described previously for azaindoles, and suggesting the cross-coupling as the limiting step. The recovering of 40% of **7aa**, after Suzuki coupling reaction, indicates that a protodeboronation is a probable side-reaction.[24] Nevertheless, the borylated compound **10a** also can be useful for other derivatives reactions.[16]

Scheme 7. C–H borylation/arylation and C–H amination of furo[2,3-*b*]pyridine core



[a]Yield determined by GC-MS, [b]Yield of isolated product

These findings encourage us to expand the functionalization studies. Recently, C–H amination of pyridine *N*-oxides has been described as a usefulmethod for the selective functionalization of the pyridines' α-positions. This reaction is carried out using a phosphonium salt and a nucleophilic amine to furnish the aminated product. Compared to furo[2,3-*b*]pyridines, the *N*-oxides derivatives are known to be more reactive toward nucleophiles and electrophiles, using classical methodologies that limit structure diversification. Therefore, we subjected furopyridine *N*-oxide derivative **11** to C–H amination under the same conditions used for pyridines (Table 2, entry 1). However, in contrast to the reported pyridine substrates,[13] a mixture of two regioisomers, **12a** and **12b**, was obtained in low yield, with higher selectivity for β-amination instead of specificity for the α-position (2:1). This unexpected site-selectivity stimulated a wider study of this reaction (Table 2). We found that, by reacting **11** with PyBroP and pyrrolidine under optimized conditions (Table 2, Entry 8), amination products **12a** and **12b** could be obtained in 97% yield (Scheme 7).

Table 2. Optimization of reaction conditions for direct amination of 11

Entry	Additive	Pyrrolidine	Solvent	Temp	Yield [%][a] (ratio 12a/12b)
1	PyBrop[b]	3 equiv	DCM	rt	34 (2:1)

2	PyBOP[c]	3 equiv	DCM	rt	23 (2:1)
3	PyBOP	-	DCM	rt	-[d]
4	DCP[e]	3 equiv	DCM	rt	-[d]
5	PyBOP	3 equiv	MeCN	rt	30 (1:1)
6	PyBOP	6 equiv	MeCN	rt	87 (1:2)
7	PyBOP	6 equiv	DCM	rt	54 (1:1)
8	PyBrop	6 equiv	MeCN	rt	97 (1:1)
9	PyBOP	3 equiv	MeCN	70°C	53 (1:2)
10	PyBOP	6 equiv	MeCN	70°C	80 (1:2)

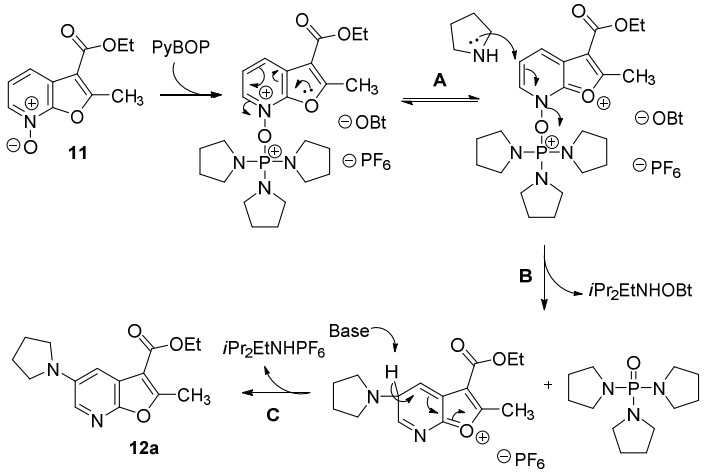
[a]Yield of isolated product after overnight reaction. [b]Bromotripyrrolidinophosphonium hexafluorophosphate. [c](Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate. [d]No conversion was observed. [e]Diethyl chlorophosphate.

Varying the phosphonium salt between PyBOP and PyBrop did not change the reactivity when DCM was used as solvent (Table 2, Entries 1 and 2). However, when the solvent was changed to MeCN, regioisomers **12a/12b** were produced equally in low yield (Table 2, Entry 5). To evaluate the importance of the pyrrolidine source, we investigated whether the pyrrolidine present in the phosphonium salt was sufficient to drive the reaction; however, no conversion of **11** was observed (Table 2, Entry 3). The use of diethyl chlorophosphate (DCP) did not afford any aminated product (Table 2, Entry 4). Higher yields were obtained using a larger excess of pyrrolidine in MeCN (Table 2, Entries 6–8 and 10), especially for the phosphonium complex with PyBrop (97%; Table 2, Entry 8). Although preliminary, the results suggest that temperature seems to have little effect on the yield or selectivity (Table 2, Entries 5, 6 and 9). On the other hand, changes in both the solvent polarity and phosphonium

salt affect both the yield and regioselectivity. Higher selectivity for **12a** was only seen in DCM, whereas **12b** was predominant only for MeCN as solvent.

Our observed preliminary results for the C–H amination reactions contradict the previously reported preference for the α-amination of pyridines,[13] which we suspect is related to the greater influence of charge effects on directing the reaction to the α-position. However, for furopyridines, β-amination is also observed, which can be explained by the charge stabilization on nitrogen due to the resonance contribution by the furan ring (Scheme 8, Pathway A). These findings represent a novel approach to β-amination of pyridines, which can be largely influenced by the fused furan ring.

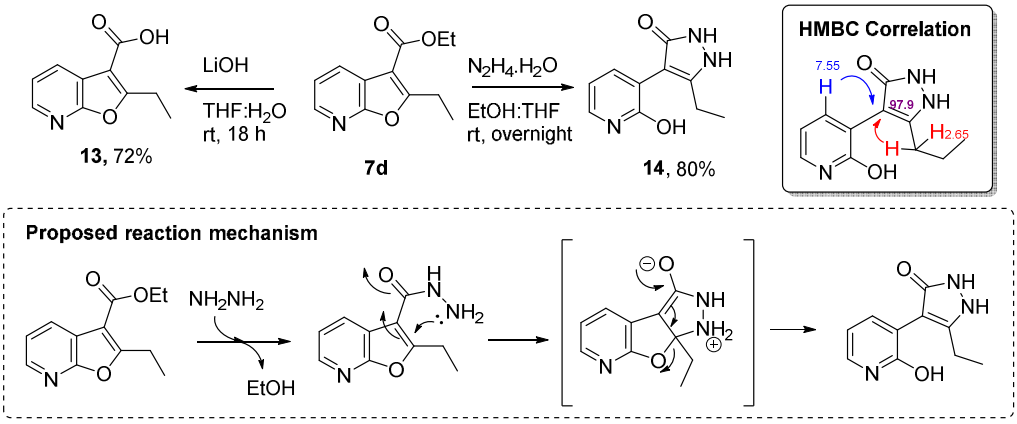
Scheme 8. Proposed reaction mechanism for the formation of 12a.



Chemical reactivity of the furan moiety of furo[2,3-*b*]pyridine core

It is well known that furo[2,3-*b*]pyridines substituted by electron-withdrawing groups undergo ring-opening reactions when treated with strong bases or nucleophiles,[9] which can be a useful strategy for producing pyridines substituted by carbocycles or heterocycles.[25] To evaluate the stability and reactivity of the compounds synthesized herein, we studied the reactions of compound **7d** with lithium hydroxide and hydrazine (Scheme 9).

Scheme 9. Chemical reactivity of furo[2,3-*b*]pyridine with nucleophilic species



In the first case, the furan ring is stable under the basic conditions, and ester hydrolysis is the prevailing process, furnishing acid derivative **13** (72%). However, a ring-opening process is observed upon reacting **7d** with hydrazine. This reaction is suggested to occur through a mechanism involving hydrazide formation (Scheme 9), followed by conjugate addition and ring-opening of the resulting tricyclic furan intermediate, affording 2-hydroxypyridinyl pyrazolone **14**. 2D NMR spectroscopy (Supporting Information) was useful in proving the structure of **14**. The HMBC experiment for **14** revealed a correlation between the *γ*-pyridine and methylene hydrogens and the carbon of the dihydropyrazolone directly bonded to position 3 of the pyridine ring (Scheme 9).

CONCLUSION

In summary, we have reported a versatile and efficient synthesis of a small library of 2-(alkyl or aryl)-3-ethylcarboxylate-furo[2,3-*b*]pyridines in good to excellent yields. In addition, the chemical reactivities of the pyridine and furan moieties of this heteroaromatic core were evaluated. Although some types of C–H activation were unsuccessful, C–H amination and C–H borylation proved to be good strategies to decorate this core. Although the scope of these reactions needs to be further investigated, some relevant findings, as *β*-amination of pyridine

moiety is unprecedented in the literature. The furan moiety in this heterocyclic scaffold is stable under basic conditions, but is very reactive toward hydrazine, furnishing a dihydropyrazolone ring system. The strategies described in this work involve an underexplored heterocycle in organic and medicinal chemistry; however, they may be applied to generate a library of fragments that could be useful in several research areas, including as valuable building blocks with potentially interesting molecular properties and activities for medicinal chemistry.

EXPERIMENTAL SECTION

General Remarks. Commercially available reagents and solvents were used without further purification. Melting points were determined in open capillary tubes using an electronic apparatus. Yields refer to isolated and purified products, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) and visualized under UV light at 254 and 365 nm. Column chromatography was performed using silica gel 60 (70–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 300, 400 or 500 MHz and 75, 101 or 126 MHz, respectively. Chemical shifts were referenced to the deuterated solvent (i.e., for $CDCl_3$, δ = 7.26 and 77.16; for DMSO-d_6, δ = 2.50 and 39.52, for ^{1}H and ^{13}C NMR, respectively) and are reported in parts per million (ppm, δ). Coupling constants (*J*) are stated in Hz using the splitting abbreviations: s, singlet; d, doublet; t, triplet; quin, quintet; hept, heptet; m, multiplet; br, broad. High-resolution mass spectra (HRMS) were measured by a TOF (Time of Flight) spectrometer, using electrospray ionization (ESI). Gas chromatography (GC) analyses were performed on a GC system coupled to a mass-selective detector with electron impact ionization (EI). Infrared (IR) spectra were measured in KBr, and wavelengths are reported in cm^{-1}.

General procedure for the synthesis of ethyl pyridinylacetate substrates 4b and 4c: To a solution of the respective 2-(pyridin-3-yl)acetic acid (4 mmol) in ethanol (30 mL) under nitrogen atmosphere was added concentrated H_2SO_4 (200 μL). The mixture was stirred at 100°C for 24 h. After cooling, the reaction mixture was concentrated to dryness and the residue was taken up in chloroform, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (8:2) to afford the desired product.

Ethyl 2-(5-bromopyridin-3-yl)acetate (**4b**): 923 mg (95%); pale yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 2.2 Hz, 1H), 8.47 (d, J = 1.7 Hz, 1H), 8.00 (t, J = 1.8 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.78 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.3, 149.0, 148.6, 139.7, 132.5, 119.7, 60.6, 36.5, 14.0; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{11}BrNO_2^+$ 243.9968; Found 243.9987.

Ethyl 2-(6-chloropyridin-3-yl)acetate (**4c**): 716 mg (90%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 8.2, 2.5 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.57 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 150.3, 150.1, 139.8, 128.8, 124.1, 61.4, 37.6, 14.1; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{11}ClNO_2^+$ 200.0473; Found 200.0475.

General procedure for the synthesis of pyridine-*N*-oxide derivatives: A solution of *m*-CPBA (4.5 mmol) in CH_3Cl (10 mL) was added dropwise to a solution of pyridine substrate (3 mmol) in CH_3Cl (10 mL) with stirring at room temperature. After overnight reaction, the solvent was removed under reduced pressure and the residue was taken up in 2 M Na_2CO_3 solution and extracted with chloroform (3 × 20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to give the desired product.

3-(2-Ethoxy-2-oxoethyl)pyridine 1-oxide (**5a**): 494 mg (91%); white solid; mp 90–92°C; NMR data according to the literature.[19]

3-Bromo-5-(2-ethoxy-2-oxoethyl)pyridine 1-oxide (**5b**): 699 mg (90%); pale yellow solid; mp 57–59°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (t, J = 1.6 Hz, 1H), 8.24 (t, J = 1.2 Hz, 1H), 7.57 (t, J = 1.3 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.74 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.7, 138.8, 138.3, 134.6, 129.7, 119.2, 60.8, 36.2, 14.0; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{11}BrNO_3^+$ 259.9917; Found 259.9924.

2-Chloro-5-(2-ethoxy-2-oxoethyl)pyridine 1-oxide (**5c**): 322 mg (50%); pale yellow solid; mp 85–87°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 1.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 8.4, 1.9 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.75 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.8, 140.8, 138.6, 132.4, 127.5, 126.6, 60.7, 36.1, 13.9; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{11}ClNO_3^+$ 216.0422; Found 216.0437.

Ethyl 2-(6-(2-ethoxyfuro[2,3-b]pyridin-3-yl)pyridin-3-yl)acetate (**7ab**): **5a** (362 mg, 2 mmol) in acetic anhydride (20 mL) was stirred at 100°C for 24 h. After cooling, the reaction mixture was concentrated to dryness and the residue was taken up in chloroform, washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (8:2) to afford the desired product **7ab** (39 mg, 0.12 mmol, 6%) as a yellow solid, mp 62–64°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.53 (dd, J = 8.0, 1.4 Hz, 1H), 8.48 (dd, J = 4.5, 1.4 Hz, 1H), 8.23 (d, J = 9.4 Hz, 1H), 7.58 (dd, J = 8.0, 4.5 Hz, 1H), 7.54 (dd, J = 9.4, 1.4 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.8, 164.2, 142.2, 140.9, 138.6, 133.2, 129.5, 123.8,

121.6, 120.5, 119.1, 118.3, 91.8, 60.5, 59.1, 36.5, 14.5, 14.0; IR (KBr) *v* 2982, 2930, 1738, 1682, 1577, 1517, 1476, 1442, 1378, 1335, 1286, 1262, 1218, 1159, 1043, 840, 800, 769, 749, 711; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2O_4^+$ 327.1339; Found 327.1364.

General procedure for the synthesis of 2,3-substituted furo[2,3-*b*]pyridines: DCM (3 mL) was added to a vial containing the pyridine-*N*-oxide substrate (0.5 mmol), DMAP (6 equiv [when acyl chlorides were used] or 2 equiv [when anhydrides were used]), and DBU (1.2 equiv). Then, the acyl source (6 equiv) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness and the residue was taken up in chloroform, washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (9:1) to afford the desired product.

Ethyl 2-methylfuro[2,3-b]pyridine-3-carboxylate (**7aa**): 80 mg (78%); white solid; mp 88–90°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (dd, J = 4.9, 1.7 Hz, 1H), 8.22 (dd, J = 7.7, 1.7 Hz, 1H), 7.43 (dd, J = 7.7, 4.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.76 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.1, 162.8, 159.8, 144.0, 130.6, 120.7, 117.8, 107.7, 60.4, 14.1, 14.0; IR (KBr) *v* 3062, 2999, 2982, 2938, 2913, 2876, 2100, 1950, 1917, 1890, 1713, 1597, 1475, 1450, 1413, 1385, 1368, 1329, 1282, 1232, 1167, 1083, 1043, 1000, 929, 862, 826, 802, 784, 764; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{12}NO_3^+$ 206.0812; Found 206.0828.

Ethyl 5-bromo-2-methylfuro[2,3-b]pyridine-3-carboxylate (**7b**): 108 mg (76%); white solid; mp 108–109°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 2.3 Hz, 1H), 8.32 (d, J = 2.1 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.82 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 163.3, 159.1, 144.8, 133.2, 120.6, 116.4, 108.4, 60.9, 14.6, 14.5; IR (KBr) *v*

3068, 2978, 2968, 2876, 2666, 2598, 2551, 1862, 1716, 1594, 1474, 1445, 1416, 1364, 1330, 1325, 1274, 1237, 1155, 1092, 1010, 944, 897, 830, 760, 707; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{11}BrNO_3^+$ 283.9917; Found 283.9931.

Ethyl 6-chloro-2-methylfuro[2,3-b]pyridine-3-carboxylate (**7c**): 109 mg (91%); white solid; mp 108–110°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.76 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 162.4, 158.4, 144.3, 133.3, 120.9, 117.1, 107.9, 60.6, 14.09, 14.00; IR (KBr) v 3087, 2987, 2912, 2876, 2550, 1959, 1825, 1721, 1582, 1480, 1439, 1387, 1370, 1310, 1238, 1193, 1116, 1082, 1000, 932, 906, 851, 827, 757, 718; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{11}ClNO_3^+$ 240.0422; Found 240.0426.

Ethyl 2-ethylfuro[2,3-b]pyridine-3-carboxylate (**7d**): 75 mg (68%); white solid; mp 50–51°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (dd, J = 4.9, 1.7 Hz, 1H), 8.27 (dd, J = 7.7, 1.7 Hz, 1H), 7.46 (dd, J = 7.7, 4.9 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.21 (q, J = 7.6 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 162.7, 159.9, 144.1, 130.8, 120.8, 117.9, 107.0, 60.4, 20.9, 14.0, 11.7; IR (KBr) v 3101, 3068, 3026, 2987, 2943, 2913, 1967, 1917, 1868, 1717, 1591, 1483, 1406, 1377, 1356, 1333, 1267, 1227, 1163, 1112, 1084, 1044, 987, 871, 806, 761; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{14}NO_3^+$ 220.0968; Found 220.0978.

Ethyl 2-propylfuro[2,3-b]pyridine-3-carboxylate (**7e**): 76 mg (65%); yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, J = 4.8, 1.7 Hz, 1H), 8.26 (dd, J = 7.7, 1.7 Hz, 1H), 7.45 (dd, J = 7.7, 4.9 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.16 (t, J = 7.4 Hz, 2H), 1.81–1.71 (dt, J = 7.4, 2H), 1.36 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 162.7, 159.9, 144.1, 130.8, 120.8, 117.8, 107.7, 60.4, 29.1, 20.7, 14.0, 13.5; IR (KBr) v

3066, 2967, 2936, 2875, 1716, 1589, 1476, 1410, 1377, 1270, 1242, 1238, 1164, 1116, 1101, 1049, 892, 806, 784, 766; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3^+$ 234.1125; Found 234.1137.

Ethyl 2-isopropylfuro[2,3-b]pyridine-3-carboxylate (**7f**): 99 mg (83%); pale yellow solid; mp 39–41°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.26 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.96 (hept, *J* = 6.9 Hz, 1H). 1.37 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.1, 162.6, 159.8, 144.1, 130.9, 120.8, 117.8, 106.0, 60.4, 26.9, 20.1, 14.0; IR (KBr) *v* 3086, 3058, 3026, 2980, 2940, 2930, 2879, 1966, 1864, 1722, 1586, 1471, 1412, 1376, 1327, 1276, 1259, 1233, 1179, 1151, 1128, 1056, 942, 873, 810, 767; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3^+$ 234.1125; Found 234.1120.

Ethyl 2-isobutylfuro[2,3-b]pyridine-3-carboxylate (**7g**): 105 mg (85%); pale yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.27 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.08 (d, *J* = 7.2 Hz, 2H), 2.15 (hept, *J* = 6.8 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.5, 162.7, 159.9, 144.2, 130.8, 120.8, 117.7, 108.3, 60.4, 27.8, 22.1, 14.0; IR (KBr) *v* 3068, 2960, 2933, 2872, 1717, 1589, 1411, 1386, 1269, 1243, 1209, 1163, 1105, 1052, 888, 803, 783, 766; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_3^+$ 248.1281; Found 248.1273.

Ethyl 2-phenylfuro[2,3-b]pyridine-3-carboxylate (**7h**): 80 mg (60%); white solid; mp 46–48°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47–8.32 (m, 2H), 8.10–7.94 (m, 2H), 7.66–7.35 (m, 4H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 159.9, 159.2, 145.2, 131.9, 131.1, 129.5, 128.3, 128.1, 121.1, 118.9,

107.8, 60.8, 13.9; IR (KBr) *v* 3100, 3062, 3032, 2982, 2908, 2872, 1970, 1923, 1875, 1718, 1607, 1587, 1567, 1474, 1447, 1404, 1372, 1284, 1256, 1226, 1177, 1091, 1086, 1053, 870, 813, 791, 779, 761, 701; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO_3^+$ 268.0968; Found 268.0989.

Ethyl 2-(p-tolyl)furo[2,3-b]pyridine-3-carboxylate (**7i**): 87 mg (62%); white solid; mp 64–66°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (dd, J = 4.8, 1.7 Hz, 1H), 8.36 (dd, J = 7.8, 1.7 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.49 (dd, J = 7.8, 4.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 2.40 (s, 1H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.5, 161.9, 161.4, 147.1, 143.2, 133.8, 131.4, 131.0, 127.4, 123.1, 121.1, 109.3, 62.8, 23.2, 16.0; IR (KBr) *v* 3091, 3034, 2982, 2905, 2857, 1920, 1719, 1603, 1583, 1553, 1506, 1472, 1407, 1369, 1317, 1285, 1259, 1218, 1192, 1089, 1053, 915, 874, 732, 802, 797, 764; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3^+$ 282.1125; Found 282.1152.

Ethyl 2-(4-fluorophenyl)furo[2,3-b]pyridine-3-carboxylate (**7j**): 71 mg (50%); white solid; mp 80–82°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (dd, J = 4.8, 1.7 Hz, 1H), 8.38 (dd, J = 7.8, 1.7 Hz, 1H), 8.16–8.08 (m, 2H), 7.51 (dd, J = 7.8, 4.8 Hz, 1H), 7.46–7.38 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.4 (164.7–162.25; d, J = 249.9 Hz), 162.3, 159.8, 158.2, 145.2, 132.1 (132.2–132.1; d, J = 9.0 Hz), 131.9, 124.7 (124.7–124.6; d, J = 3.2 Hz), 121.1, 118.8, 115.4 (115.5–115.3; d, J = 22.0 Hz), 107.7, 60.8, 13.9; IR (KBr) *v* 3084, 2982, 1723, 1610, 1573, 1505, 1473, 1407, 1376, 1289, 1260, 1235, 1159, 1082, 1052, 834, 800, 766; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{13}FNO_3^+$ 286.0874; Found 286.0884.

Ethyl 6-fluoro-2-methylfuro[2,3-b]pyridine-3-carboxylate **(8)**: To an oven-dried vial was added **7aa** (51 mg, 0.25 mmol, 1.0 equiv) and MeCN (3.0 mL). While the solution was

stirring rapidly, AgF_2 (109.5 mg, 0.75 mmol, 3.00 equiv) was added at once. The vial was sealed and stirred at 60°C for 18 h. After cooling, the reaction was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_3Cl (30 mL). The organic layer was washed once with brine (20 mL), dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (9:1) to afford the desired product **8** as a white solid (8 mg, 0.4 mmol, 15%); mp 79–81°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (t, *J* = 7.95, 1H), 6.95 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.79 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 162.9 (162.9–163.0, d, *J* = 4.2 Hz), 160.3 (158.7–161.9, d, *J* = 242.9 Hz), 157.3, 134.9 (134.9–135.0, d, *J* = 8.7 Hz), 116.0 (115.9–116.0, d, *J* = 3.9 Hz), 108.7, 105.7 (105.5–105.9, d, *J* = 36.3 Hz), 60.7, 29.7, 14.3; IR (KBr) *v* 3093, 2988, 2963, 2929, 2880, 1953, 1705, 1604, 1469, 1394, 1326, 1235, 1164, 1104, 1087, 1029, 1006, 974, 864, 834, 757; HRMS (+ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{11}FNO_3^+$ 224.0717; Found 224.0710.

***Ethyl 2-methyl-4-(4-nitrophenyl)furo[2,3-b]pyridine-3-carboxylate* (9):** To an oven-dried vial was added **7aa** (82 mg, 0.4 mmol, 1.0 equiv) and acetone (2.0 mL). While the solution was stirring, a solution of ferrocene (37 mg, 0.2 mmol, 0.5 equiv) in acetone (1.0 mL) was added dropwise during 30 min. The vial was sealed and stirred at room temperature for 18 h. The reaction mixture was concentrated to dryness and the residue was taken up in chloroform, washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (8:2) to afford the desired product **9** as a yellow solid (10 mg, 0.03 mmol, 8%); mp 121–123°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (d, *J* = 5.1 Hz, 1H), 8.34 (d, *J* = 8.8 Hz, 2H),

7.72 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 5.1 Hz, 1H), 3.77 (q, J = 7.1 Hz, 2H), 2.73 (s, 3H), 0.75 (t, J = 7.1 Hz, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4, 162.4, 160.4, 147.3, 145.1, 144.1, 141.9, 129.7, 123.2, 121.6, 114.8, 108.9, 60.3, 13.8, 13.2; IR (KBr) v 3109, 3075, 2961, 2927, 2853, 1591, 1515, 1411, 1348, 1272, 1211, 1104, 1078, 1021, 938, 870, 852, 832, 805, 756; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_5^+$ 327.0975; Found 327.0980.

Ethyl 2-methyl-5-(4-nitrophenyl)furo[2,3-b]pyridine-3-carboxylate **(10b):** Furo[2,3-*b*]pyridine **7aa** (102.5 mg, 0.5 mmol, 1 equiv), bis(pinacolato)diboron (B_2pin_2, 127 mg, 1 equiv), $[Ir(COD)OMe]_2$ (6.6 mg, 0.01 mmol, 2.0 mol%), 1,10-phenanthroline (3.6 mg, 0.02 mmol, 4.0 mol%), and dioxane (2.0 mL) were stirred at 100°C for 48 h. After cooling, the reaction mixture was concentrated to dryness and to the residue was added 4-nitrophenyltriflate 4-nitro-aryltriflate (synthesized according to the literature,[26] 135 mg, 0.5 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol,4 mol%), CyJohnPhos (2-(dicyclohexylphosphino)biphenyl ,14 mg, 0.04 mmol, 8 mol%), and LiOH (29 mg, 1.2 mmol, 2.4 equiv). In sequence to the closed vial under nitrogen atmosphere was added 3 mL of THF/H_2O (1:4). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated to dryness and the residue was taken up in chloroform, washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (8:2) to afford the desired product **10b** as a pale yellow solid (41 mg, 0.125 mmol, 25%); mp 149–151°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 2.3 Hz, 1H), 8.47 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 2.86 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 163.5, 160.9, 147.6, 144.8, 143.2, 132.1, 129.6, 128.4, 124.5, 119.3, 108.9, 61.0, 14.7, 14.5; IR (KBr) v 3119, 2987, 2965, 2920, 2851,

1711, 1604, 1502, 1468, 1421, 1395, 1349, 1316, 1264, 1215, 1159, 1089, 1033, 947, 917, 854, 803, 763, 699; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_5^+$ 327.0975; Found 327.0975.

3-(Ethoxycarbonyl)-2-methylfuro[2,3-b]pyridine 7-oxide **(11)**: The reaction was conducted via the general procedure for pyridine-*N*-oxides. The desired product was obtained after 48 h of reaction and purification by column chromatography on silica gel with DCM/MeOH (9.5:0.5), as a white solid (544 mg, 82%); mp 132–134°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (dd, *J* = 6.4, 0.9 Hz, 1H), 7.76 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.38 (dd, *J* = 7.9, 6.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 162.1, 150.3, 135.3, 122.7, 121.8, 119.5, 109.1, 60.8, 14.0, 13.9; IR (KBr) *v* 3426, 3128, 2994, 1952, 1881, 1809, 1717, 1655, 1611, 1481, 1454, 1385, 1332, 1272, 1253, 1211, 1161, 1120, 1102, 1065, 1009, 965, 873, 816, 799, 727; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{12}NO_4^+$ 222.0761; Found 222.0754.

Procedure for the C–H amination of 11: Acetonitrile (3 mL) was added to a closed vial containing **11** (66 mg, 0.3 mmol, 1.0 equiv), Bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop, 182 mg, 0.39 mmol, 1.3 equiv), and diisopropylethylamine (DIPEA, 156 μL, 0.9 mmol, 3 equiv). Then, pyrrolidine (150 μL, 1.8 mmol, 6 equiv) was added and the mixture was stirred at 70°C for 18 h. The mixture reaction was concentrated to dryness and the residue was taken up in chloroform, washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel with hexane/ethyl acetate (8:2) to afford the desired product.

Ethyl 2-methyl-5-(pyrrolidin-1-yl)furo[2,3-b]pyridine-3-carboxylate (**12a**): 38 mg (47%); pale orange solid; mp 86–88°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.7 Hz, 1H), 7.39

(d, J = 2.7 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.38–3.32 (m, 4H), 2.75 (s, 3H), 2.13–1.97 (m, 4H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 163.4, 153.9, 142.7, 129.2, 119.0, 112.2, 108.2, 60.4, 48.5, 25.5, 14.8, 14.5; IR (KBr) v 3096, 3071, 2971, 2925, 2869, 1944, 1706, 1622, 1576, 1510, 1482, 1416, 1398, 1341, 1304, 1241, 1193, 1168, 1131, 1077, 1021, 922, 808, 760, 670; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1372.

Ethyl 2-methyl-6-(pyrrolidin-1-yl)furo[2,3-b]pyridine-3-carboxylate (**12b**): 41 mg (50%); pale yellow solid, mp 81–83°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.5 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.51–3.46 (m, 4H), 2.69 (s, 3H), 2.06–1.95 (m, 4H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 160.7, 158.0, 154.9, 131.9, 108.7, 106.2, 104.0, 60.2, 47.1, 25.6, 14.5, 14.1; IR (KBr) v 3083, 3053, 2928, 2852, 1698, 1600, 1593, 1503, 1420, 1396, 1369, 1341, 1263, 1157, 1090, 1032, 985, 936, 884, 844, 805, 750; HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3^+$ 275.1390; Found 275.1383.

2-Ethylfuro[2,3-b]pyridine-3-carboxylic acid **(13)**: THF:H_2O (3 mL, 1:1) was added to a closed vial containing **7d** (87.6 mg, 0.4 mmol, 1.0 equiv) and LiOH (14.4 mg, 0.6 mmol, 1.5 equiv). The reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated to dryness and the crude material was purified by column chromatography on silica gel with hexane/MeOH/AcOH (9.8:1.5;0.5) to afford the desired product **13** (55 mg, 72%) as a white solid, mp 174–176°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.29 (dd, J = 4.9, 1.7 Hz, 1H), 8.25 (dd, J = 7.7, 1.7 Hz, 1H), 7.40 (dd, J = 7.7, 4.9 Hz, 1H), 3.19 (q, J = 7.5 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 164.4, 160.0, 143.9, 130.8, 120.6, 118.4, 107.7, 20.9, 11.9; IR (KBr) v 3428, 2962, 2925, 2853,

1710, 1599, 1481, 1414, 1261, 1174, 1088, 1030, 809, 753; HRMS (-ESI) *m*/*z*: $[M - H]^-$ Calcd for $C_{10}H_8NO_3^-$ 190.0510; Found 190.0495.

5-Ethyl-4-(2-hydroxypyridin-3-yl)-1,2-dihydro-3H-pyrazol-3-one **(14):** To a solution of **7d** (220 mg, 1 mmol, 1 equiv) in EtOH:THF (3 mL, 1:1) was added hydrazine hydrate (50–60%, 1 mL, ~18 equiv), and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated to dryness and the crude material was washed with water (5 mL), THF (10 mL), and $CHCl_3$ (10 mL) to afford the desired product **14** (164 mg, 80%) as a white solid, mp 236–238°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1H), 7.55 (dd, J = 7.2, 1.9 Hz, 1H), 7.41 (dd, J = 6.3, 1.9 Hz, 1H), 6.49 (t, J = 6.74 Hz, 1H), 2.65 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 158.9, 144.0, 137.5, 131.9, 124.4, 108.1, 97.9, 19.5, 12.6; IR (KBr) *v* 3277, 3191, 3118, 2982, 2931, 1638, 1518, 1440, 1327, 1256, 1228, 1165, 1074, 1009, 915, 872, 775; HRMS (+ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{10}H_{12}N_3O_2^+$ 206.0924; Found 206.0919.

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Supporting Information:

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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