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Oxidative cross-coupling of pyridine *N*-oxides and ethers between C(sp²)-H/C(sp³)-H bond under transition-metal-free conditions

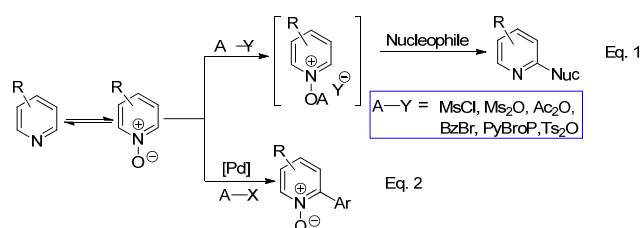
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Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

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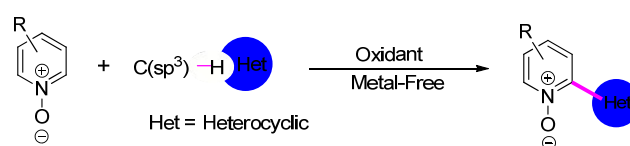
A novel and efficient method based on the cross-coupling reactions of pyridine *N*-oxides with ethers between C(sp²)-H/C(sp³)-H bonds in the presence of TBHP was developed. The strategy provides an alternative approach to pyridine moiety under transition-metal-free conditions.

Pyridine moiety are ubiquitous in natural products, pharmaceuticals and synthetic building blocks.¹ However, most of the methods for their preparation require prefunctionalization due to the low reactivity and poor regioselectivity of pyridine ring, so much efforts have been devoted to exploring the direct functionalization of *N*-activated pyridinium species, including neutral pyridinium ylides, cationic pyridinium salts, and especially pyridine *N*-oxides, which have emerged as promising alternatives for the activation and functionalization of the pyridine rings.² A number of methods for the direct α -arylation,³ alkylation,⁴ alkenylation^{1a,2d,5} of pyridine *N*-oxides, as well as introduction of halides⁶ into their structures have been developed in the presence of palladium and copper catalysts. General approaches for the synthesis of pyridine derivatives while pyridine *N*-oxides as raw material is shown in Scheme 1. One of the methods as illustrated in Eq. 1 of Scheme 1, the electrophilic character of the 2-position can be enhanced with an activating agent (A-Y), allowing for nucleophilic addition under relatively mild conditions. Unfortunately, there are quite common side reactions, including addition at the 4-position, and the direct reaction of activating agent with the nucleophile.⁷ On the other hand, the scope of the direct cross-coupling partners has broadened into aryl halides, alkenes, arylboronic acid, and so on.² In this case, the use of a transition-metal catalyst is essential both for C-H bond activation and functionalization to form C-C bond (Scheme 1, Eq. 2).



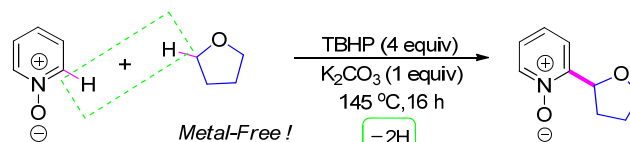
Scheme 1 General methods for the formation of pyridine derivatives from pyridine *N*-oxides

It is well known that the conversion of C-H bonds directly into C-C bonds can provide more benefits in terms of environmental sustainability and potentially lead to more efficient synthesis.⁸ Thus far, considerable development has been made in the area of oxidative C(sp)-H and C(sp²)-H cross-couplings for the various C-C bonds forming reactions.⁹ It is important to note that the oxidative couplings involving C(sp³)-H bonds have been shown the signs of progress.¹⁰ Based on the above achievements made in the area of *N*-activated pyridinium species and the conversion of C-H bonds into C-C bonds, development of a mild, general and selective method for the preparation of 2-substituted pyridines through the direct C-H functionalization is highly desirable (Scheme 2), even the cross-coupling involved C(sp³)-H bond is a challenging project in the absence of transition metal, and only one example of the reaction of pyridine *N*-oxide derivatives with alkanes has been reported.¹¹



Scheme 2 The oxidative cross-coupling of pyridine *N*-oxides with C(sp³)-H bonds under metal-free conditions

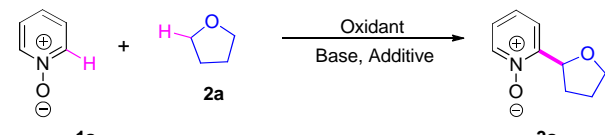
In our continuing efforts on the C-H activation and functionalization under the transition-metal-free conditions,¹² herein, we wish to disclose a direct C-2 alkylation of pyridine *N*-oxides, through a dehydrogenative C-C cross-coupling reactions between 2-position C(sp²)-H bond of pyridine *N*-oxides with α -position C(sp³)-H of ethers in the presence of *tert*-butyl hydroperoxide (TBHP) under metal-free conditions (Scheme 3). The reaction generated the good yields of the corresponding products, which are very important class of heterocycles that have numerous applications for various biologically active compounds and organic functional materials.¹³



Scheme 3 Dehydrogenative C-C cross-coupling reactions between pyridine *N*-oxides with ethers

We focused our initial investigation on the optimization of conditions for the model reaction of pyridine *N*-oxides (**1a**) with tetrahydrofuran (THF, **2a**). When the model reaction was carried out in the presence of H₂O₂, 3-chloroperoxybenzoic acid (*m*-CPBA), di(*tert*-butyl) peroxide (DTBP) or K₂S₂O₈ as oxidant, no desired cross-coupling product **3a** was observed (Table 1, entries 1–4). As *tert*-butyl hydroperoxide (TBHP, 70% aqueous) has been widely used as an efficient oxidant in the oxidative coupling reactions,^{11,12,14} we tried TBHP (2.0 equiv, 70% aqueous) as oxidant in the model reaction initially, but only 25% yield of **3a** was obtained (Table 1, entry 5). Cumyl hydroperoxide (CHP) was less effective, leading to 20% yield of **3a** (Table 1, entry 6). Further experiments showed that the product yield could be improved to 35% when the amount of TBHP was increased to fourfold (Table 1, entry 7). Then, various bases were examined for the model reaction using TBHP (70% aqueous) as an oxidant. However, organic base such as DBU failed to promote the reaction (Table 1, entry 8). The product yields were enhanced slightly when other inorganic bases including Na₂CO₃, Cs₂CO₃, *t*-BuOK, KOAc and K₂CO₃ were used, K₂CO₃ was the best one among them (Table 1, entries 9–13). To further improve the reaction efficiency, additives such as Pd(OAc)₂, CuI and FeCl₃ (10 mol%) were added to the reaction. They suppressed the transformation, and **3a** was obtained in 18%, 20%, and 21% yields, respectively (Table 1, entries 14–16). On the other hand, adding TBAB has no influence for this transformation (Table 1, entry 17). Only trace amount of **3a** was detected when TBAI was

Table 1 Optimization of the reaction conditions^a

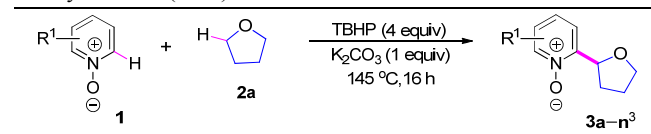


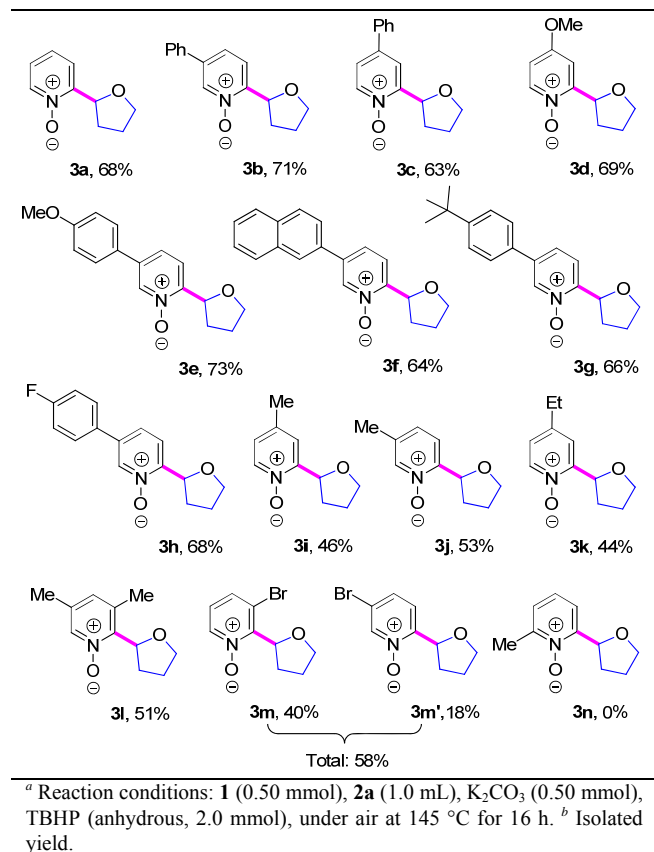
Entry	Oxidant (equiv)	Base	Additive	Yield (%) ^b
1	H ₂ O ₂ (2)	–	–	N.R.
2	<i>m</i> -CPBA (2)	–	–	N.R.
3	DTBP (2)	–	–	N.R.
4	K ₂ S ₂ O ₈ (2)	–	–	N.R.
5	TBHP (2)	–	–	25
6	CHP (2)	–	–	20
7	TBHP (4)	–	–	35
8	TBHP (4)	DBU	–	12
9	TBHP (4)	Na ₂ CO ₃	–	37
10	TBHP (4)	Cs ₂ CO ₃	–	36
11	TBHP (4)	<i>t</i> -BuOK	–	37
12	TBHP (4)	KOAc	–	45
13	TBHP (4)	K ₂ CO ₃	–	50
14	TBHP (4)	K ₂ CO ₃	Pd(OAc) ₂	18
15	TBHP (4)	K ₂ CO ₃	CuI	20
16	TBHP (4)	K ₂ CO ₃	FeCl ₃	21
17	TBHP (4)	K ₂ CO ₃	TBAB	41
18	TBHP (4)	K ₂ CO ₃	TBAI	trace
19 ^c	TBHP (4)	K ₂ CO ₃	–	68

^a Reaction conditions: **1a** (0.50 mmol), **2a** (1.0 mL, as well as solvent), base (0.50 mmol), additive (10 mol%), under air at 145 °C for 16 h. ^b Isolated yield. ^c anhydrous *tert*-butyl hydroperoxide was used. DTBP = *tert*-butyl hydroperoxide. CHP = cumyl hydroperoxide. TBAI = tetrabutylammonium iodide. TBAB = tetrabutylammonium bromide.

used as additive (Table 1, entry 18). Notably, further experiment demonstrated a reaction enhancement by using anhydrous TBHP instead of its 70% aqueous solution, providing **3a** in 68% yield (Table 1, entry 19).
 With the optimal reaction conditions in hand (in the presence of 4.0 equiv of the anhydrous TBHP at 145 °C for 16 h), the cross-coupling of a diverse range of pyridine *N*-oxides with **2a** was investigated to probe the generality of this reaction. A series of the corresponding products of pyridine *N*-oxides were then prepared through this cross-coupling reaction and the results are listed in Scheme 4. The reaction is compatible with various electronically and structurally diverse pyridine *N*-oxide derivatives with **2a**, giving the corresponding products in moderate to good yields. Pyridine *N*-oxides with an aryl group (such as Ph, *p*-MeOPh, *p*-(*t*-Bu)Ph, *p*-FPh) on the *para*- or *meta*-position reacted with **2a** to generate the cross-coupling products (**3b**, **3c**, **3e**, **3g**, **3h**) in 63–73% yields. It should be noted that 3-naphthylpyridine *N*-oxide also reacted with **2a** smoothly, providing the desired product **3f** in 64% yield. As we expected, *para*- and *meta*-alkyl(alkoxy) substituted pyridine *N*-oxides also worked well to give the corresponding products (**3d**, **3i–k**) in 46–69% yields. In addition, this reaction was applicable to the disubstituted pyridine *N*-oxide, yielding **3l** in 51% yield.

Scheme 4 Cross-coupling of pyridine *N*-oxides with tetrahydrofuran (THF)^a

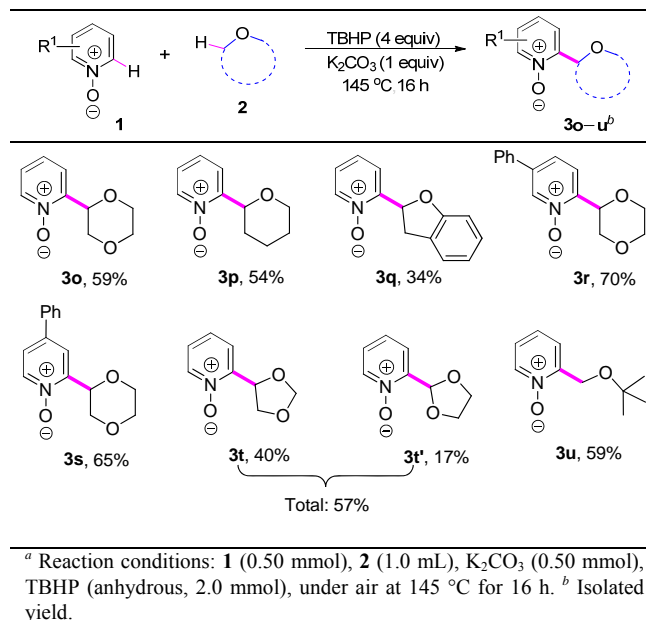




Notably, when 3-bromopyridine *N*-oxide was employed, a total 58% yield of the isomer products **3m** and **3m'** was achieved with 20:19 ratio. The C–H activation mainly occurred at the more steric demanding 2-position to afford the product **3m** in 40% yield, and the lower steric demanding 6-position to afford the product **3m'** in 18% yield. Surprisingly, for the substrate in which methyl group located at the *ortho*-position of pyridine *N*-oxide, no target product **3n** was obtained.

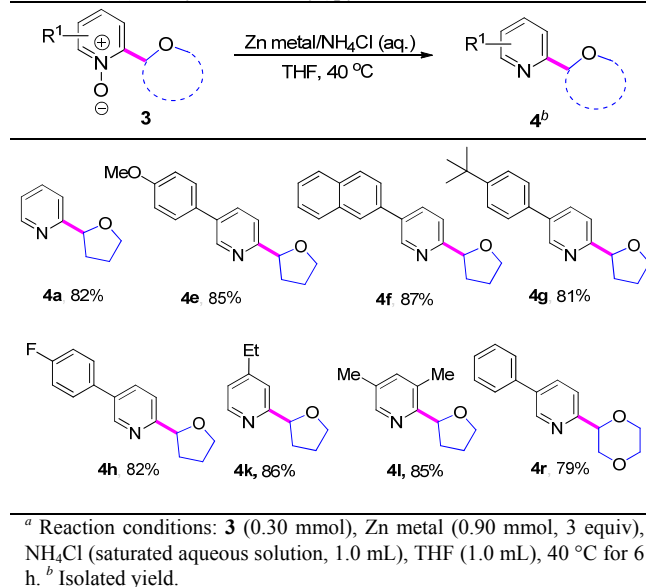
The reactions of pyridine *N*-oxides and various ethers were investigated. It can be seen that a range of ethers, such as 1,4-dioxane and tetrahydro-2*H*-pyran participated in the reaction with pyridine *N*-oxide (**1a**), 54–59% yields of the corresponding products (**3o** and **3p**) were achieved as shown in Scheme 5. However, the reaction of 2,3-dihydrobenzofuran with **1a** provided the desired product **3q** only in 34% yield. Simultaneously, in order to expand the scope of pyridine *N*-oxides, 3-phenylpyridine-1-oxide and 4-phenylpyridine-1-oxide were surveyed through the dehydrogenative cross-coupling reactions with 1,4-dioxane in the presence of TBHP, which proceeded smoothly to generate the corresponding products **3r** and **3s** in 70% and 65% yields, respectively. It should be noted that there are two kinds of α -position C(sp³)–H bonds adjacent to an oxygen atom in 1,3-dioxolane, leading to two region-isomer products **3t** and **3t'**, in 40:17 ratio. The results indicated that the electronic property of ether influences its regioselectivity. On the other hand, chain ether, such as *tert*-butyl methyl ether was compatible in this transformation, providing the corresponding product **3u** in 59% yield.

Scheme 5 The scope of ethers with the reaction of pyridine *N*-oxides



With the obtained products, such as **3a**, **3e**, **3f**, **3g** and so on in hand, which were easily reduced under mild conditions. As selected examples (**3a**, **3e**, **3f**, **3g**, **3h**, **3k**, **3l** and **3r**) in Scheme 6, they could be reduced by Zn metal powder and NH₄Cl (saturated aqueous solution) in THF¹⁵ to generate the corresponding deoxygenation product pyridines (**4a**, **4e**, **4f**, **4g**, **4h**, **4k**, **4l** and **4r**) in 79–87% yields (Scheme 6).

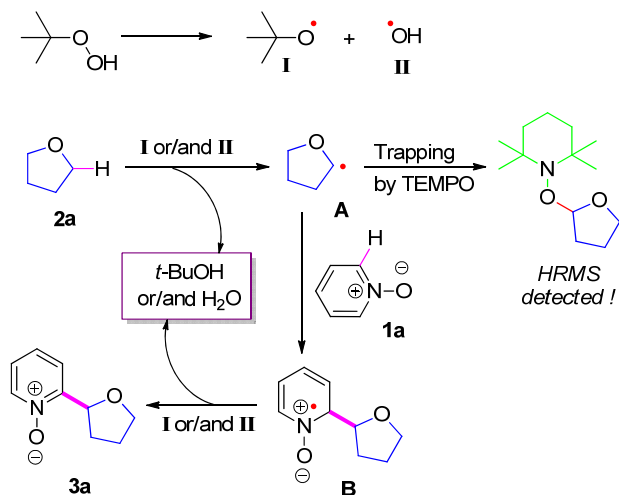
Scheme 6 Deoxygenation of 2-(tetrahydrofuran-2-yl)pyridine *N*-oxides to 2-(tetrahydrofuran-2-yl)pyridines^a



When 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) was added (2.0 equiv) in the model reaction under the present reaction conditions, the reaction was completely shut down. It is suggested that TEMPO acts as a radical scavenger and the reaction involves a radical process.¹⁶ A plausible mechanism for this reaction is proposed in Scheme 7. At first, a *tert*-butoxy radical (**I**) and a hydroxyl radical (**II**) were generated from a homolytic cleavage of *tert*-butyl hydroperoxide (TBHP). Then

THF (**2a**) underwent a hydrogen abstraction of C–H bond adjacent to its oxygen atom in the presence of **I** or/and **II** to get the corresponding free radical **A**. Addition of **A** to pyridine *N*-oxide generated the radical **B**.¹⁷ Finally, the desired product **3a** was formed through the reaction of the intermediate **B** with **I** or/and **II**. The proposed mechanism was further investigated through the trapping of free radical **A** with TEMPO by HPLC-HRMS probe. The coupling product of **A** with TEMPO was confirmed by HRMS.

Scheme 7 The proposed reaction mechanism



In summary, we have developed a novel and efficient method for the preparation of biheterocycles from pyridine *N*-oxides and simple ethers via intermolecular dehydrogenative reaction between between C(sp²)-H/C(sp³)-H bond in the presence of TBHP. Moreover, the obtained 2-substituted pyridine *N*-oxides could be reduced to the 2-substituted pyridines under mild reduction conditions. This strategy provides an alternative approach to 2-substituted pyridine moiety under transition-metal-free conditions. The detail mechanism investigation and further application of this protocol is underway in our laboratory.

Experimental Section

All operations are carried out in a glove box under nitrogen atmosphere. All ¹H NMR and ¹³C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometers (400 MHz or 100 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the product were collected on a Waters Micromass GCT instrument. High resolution mass spectroscopy data of the product were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI).

The chemicals and solvents were purchased from commercial suppliers either from Aldrich (USA) or Shanghai Chemical Company (China) without further purification. All the solvents were dried and freshly distilled prior to use. All the reactions

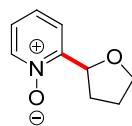
were carried out under air atmosphere. Products were purified by flash chromatography on 100–200 mesh silica gels, SiO₂.

Typical procedure for the cross-coupling of pyridine 1-oxide with tetrahydrofuran

To a 25 mL Schlenk tube were added pyridine 1-oxide (0.50 mmol), anhydrous *tert*-butyl hydroperoxide (TBHP, 2.0 mmol, 4.0 equiv) and K₂CO₃ (0.50 mmol, 1.0 equiv). Then tetrahydrofuran (THF, 1.0 mL) was injected into bottom of the tube using a long needle syringe. The mixture was stirred at the preheated oil bath under 140 °C for 16 h. When the reaction was cooled down to room temperature, the mixture was filtered through a short plug of silica gel and washed with ethyl ether (3×6.0 mL) and saturated NaCl solution (3×6.0 mL). The combined organic phase was dried over MgSO₄ and then concentrated under vacuum. The product was purified through flash column chromatography on 200–300 mesh silica gel with petroleum ether/ethyl acetate as eluent with a suitable ratio according to the TLC analysis.

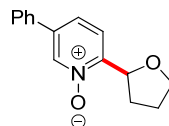
General procedure for deoxidizative reaction

According to the procedure reported in the literature (Y. Aoyagi, T. Abe and A. Ohta, *Synthesis*, 1997, 891), a 20 mL vial was charged with 2-substituted pyridine *N*-oxide (0.30 mmol, 1.0 equiv), THF (1.0 mL) and saturated NH₄Cl aqueous solution (1.0 mL). After the mixture was stirred under an air atmosphere at 40 °C for 30 minutes, Zn⁰ powder (0.90 mmol, 3.0 equiv) in 4 portions of 0.75 eq. each in 20 minutes interval was added. When the reaction was complete by TLC analysis, the mixture was filtered to remove unreacted Zn⁰ and filter cake was washed with THF. The mixture was diluted with EtOAc and organic layer was separated. The organic phase was washed with H₂O (2×5.0 mL), dried with MgSO₄, filtered and concentrated in vacuo. The residue is then purified via silica gel chromatography using petroleum ether/ethyl acetate mixtures.



2-(Tetrahydrofuran-2-yl)pyridine 1-oxide (**3a**)

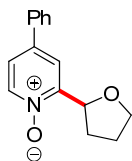
Colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ: 8.22 (d, *J* = 6.32 Hz, 1H), 7.53 (d, *J* = 7.68 Hz, 1H), 7.32–7.28 (m, 1H), 7.21–7.17 (m, 1H), 5.36 (t, *J* = 6.42 Hz, 1H), 4.13–4.08 (m, 1H), 4.00–3.94 (m, 1H), 2.75–2.66 (m, 1H), 2.07–1.99 (m, 1H), 1.92–1.81 (m, 2H); ¹³C NMR (100 Mz, CDCl₃) δ: 139.4, 126.2, 123.8, 122.5, 75.3, 69.1, 30.9, 25.6. HRMS (ESI) ([M+H]⁺) Calcd. For C₉H₁₂NO₂: 166.0868, Found: 166.0868.



5-Phenyl-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (**3b**)

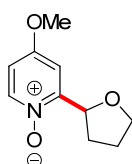
Yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ: 8.49 (s, 1H), 7.58–7.56 (m, 1H), 7.54–7.51 (m, 3H), 7.49–7.41 (m, 4H), 5.40 (t, *J* = 6.04 Hz, 1H), 4.14–4.11 (m, 1H), 4.01–3.96 (m, 1H), 2.76–2.70

(m, 1H), 2.04 (br, 1H), 1.90 (br, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 152.2, 138.1, 137.6, 135.3, 129.2, 129.0, 126.8, 125.0, 122.4, 75.3, 69.1, 31.0, 25.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{15}\text{NO}_2$: 242.1181, Found: 242.1179. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{16}\text{NO}_2$: 242.1181, Found: 242.1179.



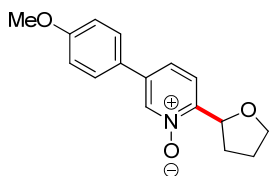
4-Phenyl-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3c)

Yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.24 (d, $J = 6.72$ Hz, 1H), 7.75 (s, 1H), 7.62 (d, $J = 7.60$ Hz, 2H), 7.49–7.46 (m, 2H), 7.43–7.40 (m, 2H), 5.39 (t, $J = 6.44$ Hz, 1H), 4.18–4.12 (m, 1H), 4.02–3.97 (m, 1H), 2.80–2.72 (m, 1H), 2.09–2.01 (m, 1H), 1.96–1.85 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 153.7, 139.4, 138.7, 136.8, 129.2, 128.9, 126.5, 121.5, 120.0, 75.4, 69.1, 31.0, 25.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{16}\text{NO}_2$: 242.1181, Found: 242.1176.



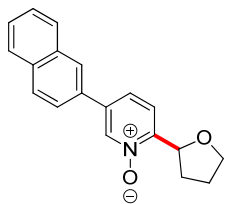
4-Methoxy-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3d)

Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.08 (d, $J = 6.84$ Hz, 1H), 7.03 (s, 1H), 6.70–6.69 (m, 1H), 5.31 (br, 1H), 4.09–4.08 (m, 1H), 3.95–3.94 (m, 1H), 3.84 (s, 3H), 2.72–2.71 (m, 1H), 2.00 (br, 1H), 1.85 (br, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 158.1, 154.8, 140.2, 110.4, 107.2, 75.4, 69.1, 55.9, 31.0, 25.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{10}\text{H}_{14}\text{NO}_3$: 196.0974, Found: 196.0971.



5-(4-Methoxyphenyl)-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3e)

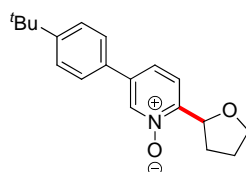
White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.41 (s, 1H), 7.52 (d, $J = 8.24$ Hz, 1H), 7.47–7.41 (m, 3H), 6.98 (d, $J = 8.56$ Hz, 2H), 5.39 (t, $J = 5.82$ Hz, 1H), 4.15–4.10 (m, 1H), 4.00–3.94 (m, 1H), 3.84 (s, 3H), 2.73–2.68 (m, 1H), 2.06–1.99 (m, 1H), 1.92–1.83 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 160.3, 137.6, 137.1, 127.9, 127.6, 124.3, 122.2, 114.6, 75.2, 69.1, 55.3, 31.0, 25.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{16}\text{H}_{18}\text{NO}_3$: 272.1287, Found: 272.1285.



5-(Naphthalen-2-yl)-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3f)

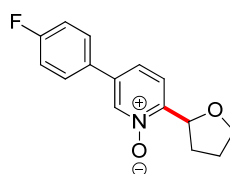
Colourless solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.60 (s, 1H), 8.01 (s, 1H), 7.96 (d, $J = 8.52$ Hz, 1H), 7.92–7.88 (m, 2H), 7.64

(dd, $J_1 = 8.56$ Hz, $J_2 = 1.28$ Hz, 1H), 7.61 (br, 2H), 7.57–7.53 (m, 2H), 5.46–5.43 (m, 1H), 4.19–4.14 (m, 1H), 4.04–3.99 (m, 1H), 2.80–2.71 (m, 1H), 2.11–2.03 (m, 1H), 1.98–1.88 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 152.3, 138.0, 137.8, 133.4, 133.2, 132.6, 129.2, 128.3, 127.7, 126.9, 126.8, 126.2, 124.8, 124.2, 122.5, 75.4, 69.2, 31.0, 25.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{19}\text{H}_{18}\text{NO}_2$: 292.1338, Found: 292.1335.



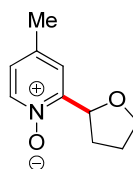
5-(4-tert-Butylphenyl)-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3g)

White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.47 (s, 1H), 7.56 (d, $J = 8.24$ Hz, 1H), 7.52–7.47 (m, 5H), 5.43–5.39 (m, 1H), 4.17–4.11 (m, 1H), 4.02–3.97 (m, 1H), 2.76–2.71 (m, 1H), 2.10–2.01 (m, 1H), 1.97–1.90 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (100 Mz, CDCl_3) δ : 152.3, 151.9, 137.9, 137.4, 132.4, 126.5, 126.2, 124.6, 122.3, 75.3, 69.1, 34.7, 31.2, 31.0, 25.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{19}\text{H}_{24}\text{NO}_2$: 298.1807, Found: 298.1803.



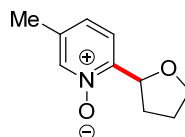
5-(4-Fluorophenyl)-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3h)

Yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.41 (s, 1H), 7.56 (d, $J = 8.20$ Hz, 1H), 7.51–7.48 (m, 2H), 7.42 (d, $J = 8.20$ Hz, 1H), 7.18–7.14 (m, 2H), 5.38 (t, $J = 6.38$ Hz, 1H), 4.15–4.10 (m, 1H), 4.01–3.95 (m, 1H), 2.75–2.69 (m, 1H), 2.11–2.00 (m, 1H), 1.95–1.84 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 163.3 (d, $J_{\text{C-F}} = 247.91$ Hz), 152.3, 137.4, 137.1, 131.5 (d, $J_{\text{C-F}} = 3.41$ Hz), 128.6 (d, $J_{\text{C-F}} = 8.31$ Hz), 124.4, 122.5, 116.3 (d, $J_{\text{C-F}} = 21.74$ Hz), 75.3, 69.1, 31.0, 25.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{15}\text{FNO}_2$: 260.1087, Found: 260.1087.



4-Methyl-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3i)

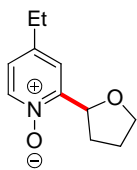
Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.08 (d, $J = 6.52$ Hz, 1H), 7.31 (s, 1H), 6.97–6.96 (m, 1H), 5.33 (t, $J = 6.60$ Hz, 1H), 4.12–4.07 (m, 1H), 3.98–3.92 (m, 1H), 2.74–2.65 (m, 1H), 2.34 (s, 3H), 2.06–1.96 (m, 1H), 1.92–1.78 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 153.0, 138.7, 137.6, 124.5, 123.0, 75.3, 69.1, 31.0, 25.6, 20.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{10}\text{H}_{14}\text{NO}_2$: 180.1025, Found: 180.1025.



5-Methyl-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3j)

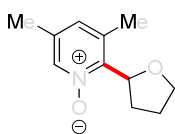
Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.06 (s, 1H), 7.38 (d, $J = 8.08$ Hz, 1H), 7.10 (d, $J = 8.04$ Hz, 1H), 5.33 (t, $J =$

6.48 Hz, 1H), 4.11–4.06 (m, 1H), 3.97–3.92 (m, 1H), 2.72–2.62 (m, 1H), 2.28 (s, 3H), 2.05–1.95 (m, 1H), 1.91–1.78 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 151.0, 139.2, 134.3, 127.3, 121.9, 75.3, 69.0, 31.0, 25.5, 17.9. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{10}\text{H}_{14}\text{NO}_2$: 180.1025, Found: 180.1024.



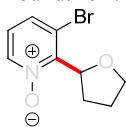
4-Ethyl-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3k)

Yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.11 (d, $J = 6.52$ Hz, 1H), 7.33 (s, 1H), 7.00 (d, $J = 5.16$ Hz, 1H), 5.35 (t, $J = 6.46$ Hz, 1H), 4.14–4.09 (m, 1H), 4.00–3.94 (m, 1H), 2.76–2.70 (m, 1H), 2.65 (q, $J = 7.53$ Hz, 2H), 2.07–1.97 (m, 1H), 1.93–1.80 (m, 2H), 1.25 (t, $J = 7.54$ Hz, 3H); ^{13}C NMR (100 Mz, CDCl_3) δ : 153.1, 143.6, 138.9, 123.2, 121.7, 75.3, 69.1, 30.9, 27.7, 25.6, 14.3. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{11}\text{H}_{16}\text{NO}_2$: 194.1181, Found: 194.1183.



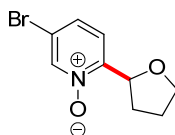
3,5-Dimethyl-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3l)

Colourless solid. ^1H NMR (400 MHz, CDCl_3) δ : 7.94 (s, 1H), 6.85 (s, 1H), 5.73 (t, $J = 7.92$ Hz, 1H), 4.10–4.04 (m, 1H), 3.93–3.88 (m, 1H), 2.56–2.48 (m, 1H), 2.39 (s, 3H), 2.21 (s, 3H), 2.10–2.00 (m, 2H), 1.93–1.83 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 148.0, 137.4, 134.6, 133.2, 130.7, 75.5, 68.5, 29.9, 26.6, 18.9, 17.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{11}\text{H}_{16}\text{NO}_2$: 194.1181, Found: 194.1180.



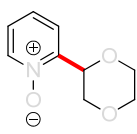
3-Bromo-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3m)

Yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 7.38 (d, $J = 5.96$ Hz, 1H), 7.20–7.17 (m, 2H), 5.37 (t, $J = 6.72$ Hz, 1H), 4.12–4.07 (m, 1H), 3.98–3.93 (m, 1H), 2.75–2.66 (m, 1H), 2.05–1.95 (m, 1H), 1.91–1.78 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 153.8, 148.9, 125.2, 124.2, 120.0, 75.6, 69.0, 31.0, 25.6. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_9\text{H}_{11}\text{BrNO}_2$: 243.9973, Found: 243.9972.



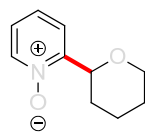
5-Bromo-2-(tetrahydrofuran-2-yl)pyridine 1-oxide (3m')

Yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.33 (s, 1H), 7.38 (br, 2H), 5.24 (t, $J = 6.42$ Hz, 1H), 4.10–4.05 (m, 1H), 3.97–3.91 (m, 1H), 2.71–2.61 (m, 1H), 2.06–1.95 (m, 1H), 1.89–1.76 (m, 2H); ^{13}C NMR (100 Mz, CDCl_3) δ : 153.0, 140.6, 128.6, 122.8, 117.9, 75.1, 69.1, 30.7, 25.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_9\text{H}_{11}\text{BrNO}_2$: 243.9973, Found: 243.9966.



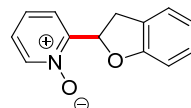
2-(1,4-Dioxan-2-yl)pyridine 1-oxide (3o)

Colourless solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (d, $J = 6.36$ Hz, 1H), 7.56 (d, $J = 7.76$ Hz, 1H), 7.32–7.29 (m, 1H), 7.23–7.19 (m, 1H), 5.31–5.28 (m, 1H), 4.52–4.83 (m, 1H), 3.97 (d, $J = 6.24$ Hz, 2H), 3.84–3.81 (m, 1H), 3.75–3.67 (m, 1H), 3.24–3.19 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 148.9, 139.3, 125.9, 124.5, 123.9, 72.2, 68.6, 67.2, 66.4. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_9\text{H}_{12}\text{NO}_3$: 182.0817, Found: 182.0815.



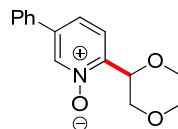
2-(Tetrahydro-2H-pyran-2-yl)pyridine 1-oxide (3p)

Colourless solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (d, $J = 6.40$ Hz, 1H), 7.55 (dd, $J = 7.84$ Hz, $J = 1.44$ Hz, 1H), 7.31–7.30 (m, 1H), 7.19–7.15 (m, 1H), 5.00–4.98 (m, 1H), 4.18–4.15 (m, 1H), 3.71–3.65 (m, 1H), 2.45–2.42 (m, 1H), 1.94–1.91 (m, 1H), 1.82–1.79 (m, 2H), 1.64–1.61 (m, 1H), 1.26–1.20 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 139.2, 126.0, 123.7, 123.1, 73.7, 68.9, 29.6, 25.9, 23.1. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{10}\text{H}_{14}\text{NO}_2$: 180.1025, Found: 108.1028.



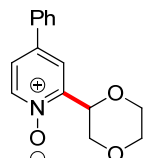
2-(2,3-Dihydrobenzofuran-2-yl)pyridine 1-oxide (3q)

Yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.28 (d, $J = 6.12$ Hz, 1H), 7.54 (dd, $J_1 = 7.72$ Hz, $J_2 = 1.28$ Hz, 1H), 7.32–7.28 (m, 1H), 7.26–7.23 (m, 1H), 7.20–7.17 (m, 2H), 6.96 (d, $J = 8.28$ Hz, 1H), 6.93–6.90 (m, 1H), 6.20–6.16 (m, 1H), 4.04–3.97 (m, 1H), 3.19–3.13 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 159.0, 139.5, 128.2, 126.1, 125.9, 125.3, 124.4, 122.7, 121.4, 109.5, 78.0, 35.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{13}\text{H}_{12}\text{NO}_2$: 214.0868, Found: 214.0861.



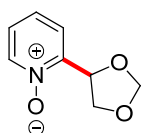
2-(1,4-Dioxan-2-yl)-5-phenylpyridine 1-oxide (3r)

Colourless solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.44 (s, 1H), 7.60 (d, $J = 8.24$ Hz, 1H), 7.53–7.44 (m, 6H), 5.36–5.33 (m, 1H), 4.56–4.52 (m, 1H), 3.99 (d, $J = 6.12$ Hz, 2H), 3.86–3.83 (m, 1H), 3.77–3.68 (m, 1H), 3.29–3.24 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 147.1, 138.7, 137.4, 135.1, 129.3, 129.1, 126.8, 124.5, 123.7, 72.2, 68.7, 67.2, 66.4. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{16}\text{NO}_3$: 258.1130, Found: 258.1124.

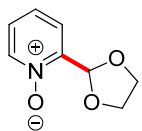


2-(1,4-Dioxan-2-yl)-4-phenylpyridine 1-oxide (3s)

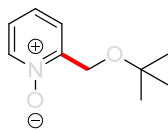
White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.23 (d, $J = 6.76$ Hz, 1H), 7.81–7.80 (m, 1H), 7.63 (d, $J = 7.32$ Hz, 2H), 7.51–7.47 (m, 2H), 7.45–7.41 (m, 2H), 5.36–5.34 (m, 1H), 4.58–4.55 (m, 1H), 4.01 (d, $J = 6.12$ Hz, 2H), 3.87–3.84 (m, 1H), 3.79–3.71 (m, 1H), 3.31–3.26 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 148.7, 139.3, 138.7, 136.5, 129.2, 129.0, 126.5, 122.1, 121.5, 72.4, 68.8, 67.3, 66.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{16}\text{NO}_3$: 258.1130, Found: 258.1127.


2-(1,3-Dioxolan-4-yl)pyridine 1-oxide (3t)

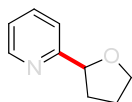
Yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (d, $J = 6.48$ Hz, 1H), 7.52 (d, $J = 7.80$ Hz, 1H), 7.32–7.29 (m, 1H), 7.24–7.20 (m, 1H), 5.40 (d, $J = 6.16$ Hz, 1H), 5.20 (s, 1H), 5.03 (s, 1H), 4.48–4.44 (m, 1H), 3.93–3.90 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 150.9, 139.0, 125.9, 124.4, 122.6, 95.5, 70.8 (d, $J = 232.18$ Hz), 65.4 (d, $J = 13.83$ Hz). HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_8\text{H}_{10}\text{NO}_3$: 168.0661, Found: 168.0665.


2-(1,3-Dioxolan-2-yl)pyridine 1-oxide (3t')

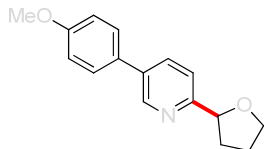
Yellow solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.24–8.22 (m, 1H), 7.56–7.54 (m, 1H), 7.26 (br, 2H), 6.36 (s, 1H), 4.09 (br, 4H); ^{13}C NMR (100 Mz, CDCl_3) δ : 147.5, 139.8, 125.8, 125.3, 123.6, 97.3, 65.4. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_8\text{H}_{10}\text{NO}_3$: 168.0661, Found: 168.0658.


2-(tert-Butoxymethyl)pyridine 1-oxide (3u)

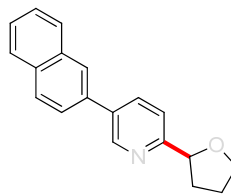
Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.23 (br, 1H), 7.61 (d, $J = 7.00$ Hz, 1H), 7.30–7.27 (m, 1H), 7.18 (br, 1H), 4.71 (s, 2H), 1.31 (s, 9H); ^{13}C NMR (100 Mz, CDCl_3) δ : 138.8, 125.8, 123.4, 123.3, 74.3, 58.8, 27.5. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{10}\text{H}_{16}\text{NO}_2$: 182.1181, Found: 182.1179.


2-(Tetrahydrofuran-2-yl)pyridine (4a)

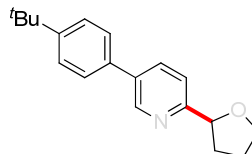
Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.52 (d, $J = 3.36$ Hz, 1H), 7.66–7.62 (m, 1H), 7.41 (d, $J = 7.80$ Hz, 1H), 7.14–7.11 (m, 1H), 5.00 (t, $J = 6.06$ Hz, 1H), 4.11–4.06 (m, 1H), 3.98–3.93 (m, 1H), 2.41–2.38 (m, 1H), 1.97–1.96 (m, 3H); ^{13}C NMR (100 Mz, CDCl_3) δ : 162.9, 148.9, 136.5, 121.9, 119.7, 81.2, 68.9, 32.9, 25.7. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_9\text{H}_{12}\text{NO}$: 150.0919, Found: 150.0921.


5-(4-Methoxyphenyl)-2-(tetrahydrofuran-2-yl)pyridine (4e)

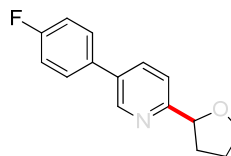
White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.75 (s, 1H), 7.82 (d, $J = 8.00$ Hz, 1H), 7.52–7.47 (m, 3H), 7.01 (d, $J = 8.20$ Hz, 2H), 5.07 (t, $J = 6.16$ Hz, 1H), 4.16–4.11 (m, 1H), 4.03–3.98 (m, 1H), 3.86 (s, 3H), 2.49–2.39 (m, 1H), 2.09–2.00 (m, 3H); ^{13}C NMR (100 Mz, CDCl_3) δ : 161.0, 159.6, 147.1, 134.6, 134.4, 130.2, 128.1, 119.7, 114.5, 81.2, 69.0, 55.3, 33.0, 25.8. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{16}\text{H}_{18}\text{NO}_2$: 256.1338, Found: 256.1340.


5-(Naphthalen-2-yl)-2-(tetrahydrofuran-2-yl)pyridine (4f)

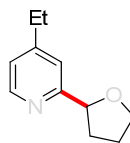
White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.92 (s, 1H), 8.05 (s, 1H), 8.02–7.89 (m, 4H), 7.72 (d, $J = 8.36$ Hz, 1H), 7.58–7.53 (m, 3H), 5.14–5.10 (m, 1H), 4.20–4.15 (m, 1H), 4.06–4.01 (m, 1H), 2.53–2.47 (m, 1H), 2.13–2.03 (m, 3H); ^{13}C NMR (100 Mz, CDCl_3) δ : 161.9, 147.7, 135.2, 135.1, 135.0, 133.6, 132.8, 128.8, 128.2, 127.7, 126.6, 126.3, 126.0, 125.1, 119.8, 81.2, 69.1, 33.1, 25.8. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{19}\text{H}_{18}\text{NO}$: 276.1388, Found: 276.1393.


5-(4-(tert-Butyl)phenyl)-2-(tetrahydrofuran-2-yl)pyridine (4g)

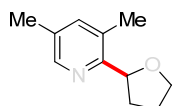
Colourless solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.79 (s, 1H), 7.87 (d, $J = 7.88$ Hz, 1H), 7.55–7.50 (m, 5H), 5.08 (t, $J = 6.46$ Hz, 1H), 4.18–4.12 (m, 1H), 4.04–3.99 (m, 1H), 2.52–2.41 (m, 1H), 2.11–2.01 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (100 Mz, CDCl_3) δ : 161.4, 151.0, 147.4, 134.9, 134.8, 134.8, 126.7, 126.0, 119.8, 81.2, 69.1, 34.6, 33.0, 31.3, 25.8. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{19}\text{H}_{24}\text{NO}$: 282.1858, Found: 282.1856.


5-(4-Fluorophenyl)-2-(tetrahydrofuran-2-yl)pyridine (4h)

Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.73 (s, 1H), 7.83 (d, $J = 8.08$ Hz, 1H), 7.56–7.51 (m, 3H), 7.19–7.15 (m, 2H), 5.08 (t, $J = 6.32$ Hz, 1H), 4.17–4.12 (m, 1H), 4.04–3.99 (m, 1H), 2.50–2.41 (m, 1H), 2.09–1.98 (m, 3H); ^{13}C NMR (100 Mz, CDCl_3) δ : 162.8 (d, $J_{\text{C-F}} = 247.82$ Hz), 161.8, 147.3, 134.8, 134.0 (d, $J_{\text{C-F}} = 17.60$ Hz), 128.7 (dd, $J_{\text{C-F}} = 8.07$ Hz, $J_{\text{C-F}} = 1.90$ Hz), 119.8 (d, $J_{\text{C-F}} = 1.84$), 116.1, 115.9 (d, $J_{\text{C-F}} = 1.89$ Hz), 81.1, 69.1 (d, $J_{\text{C-F}} = 1.80$ Hz), 33.0 (d, $J_{\text{C-F}} = 1.78$ Hz), 25.8 (d, $J_{\text{C-F}} = 1.89$ Hz). HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{15}\text{FNO}$: 244.1138, Found: 244.1132.


4-Ethyl-2-(tetrahydrofuran-2-yl)pyridine (4k)

Colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.38 (d, $J = 4.84$ Hz, 1H), 7.24 (s, 1H), 6.95 (d, $J = 4.60$ Hz, 1H), 4.95 (t, $J = 6.30$ Hz, 1H), 4.10–4.04 (m, 1H), 3.96–3.90 (m, 1H), 2.60 (q, $J = 7.59$ Hz, 2H), 2.43–2.32 (m, 1H), 1.94 (br, 3H), 1.20 (q, $J = 7.58$ Hz, 3H); ^{13}C NMR (100 Mz, CDCl_3) δ : 162.6, 153.5, 148.8, 121.6, 119.2, 81.2, 68.8, 32.9, 28.2, 25.6, 14.2. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{11}\text{H}_{16}\text{NO}$: 178.1232, Found: 178.1234.

**3,5-Dimethyl-2-(tetrahydrofuran-2-yl)pyridine (4l)**

Yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ : 8.26 (s, 1H), 7.25 (s, 1H), 5.10 (t, $J = 7.08$ Hz, 1H), 4.15–4.10 (m, 1H), 3.94–3.89 (m, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 2.24–2.17 (m, 2H), 2.15–2.09 (m, 1H), 2.06–1.96 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 155.5, 147.0, 138.8, 131.6, 130.5, 78.4, 68.6, 30.5, 26.2, 18.2, 17.9. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{11}\text{H}_{16}\text{NO}$: 178.1232, Found: 178.1231.

**2-(1,4-Dioxan-2-yl)-5-phenylpyridine (4r)**

White solid. ^1H NMR (400 MHz, CDCl_3) δ : 8.79 (s, 1H), 7.91 (d, $J = 7.92$ Hz, 1H), 7.58 (d, $J = 7.48$ Hz, 2H), 7.54 (d, $J = 8.12$ Hz, 1H), 7.51–7.47 (m, 2H), 7.43–7.40 (m, 1H), 4.83–4.80 (m, 1H), 4.21–4.18 (m, 1H), 4.03–3.95 (m, 2H), 3.86–3.75 (m, 2H), 3.62–3.57 (m, 1H); ^{13}C NMR (100 Mz, CDCl_3) δ : 156.6, 147.5, 137.6, 135.8, 135.1, 129.1, 128.1, 127.1, 120.7, 78.0, 71.2, 67.0, 66.4. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. For $\text{C}_{15}\text{H}_{16}\text{NO}_2$: 242.1181, Found: 242.1185.

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Notes and reference

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