Synthesis Y. Gao et al. Paper

Synthesis of Asymmetrical 2,6-Diarylpyridines from Linear α,β,γ,δ-Unsaturated Ketones by Addition of Ammonium Formate Followed by Annulation

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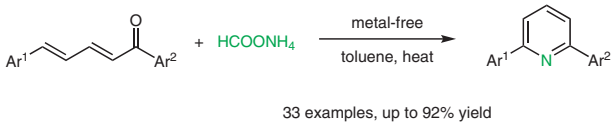
In memory of Professor Yongmin Zhang (1932–2019)



33 examples, up to 92% yield

Received: 05.06.2019
Accepted after revision: 24.07.2019
Published online: 08.08.2019
DOI: 10.1055/s-0037-1610725; Art ID: ss-2019-h0317-op

Abstract A simple and efficient method has been established for the synthesis of asymmetrical 2,6-diarylpyridines by cyclization of α,β,γ,δ-unsaturated ketones with ammonium formate under air atmosphere. The reaction is metal-free and operationally convenient from readily available starting materials. Thirty-three examples have been presented, most of which show good yields.

Key words regioselectivity, Michael addition, annulations, 2,4-dien-1-one, asymmetrical pyridine

Pyridine is one of the most important heterocycles and the pyridine structures are widely found in many natural products,[1] functional materials,[2] electrochemicals,[3] agrochemicals,[4] pharmaceutical drugs,[5,6] and organocatalysis.[7] As a sequence, the development of effective methods for constructing the pyridine skeleton has attracted considerable attention and a wide range of versatile methods have been developed in the past decades, which include the Hantzsch synthesis,[8] the Vilsmeier–Haack reaction,[9] the Chichibabin reaction,[10] the Bohlmann–Rahtz synthesis,[11] and the Krohnke synthesis.[6,12] These methods or their modified procedures are very useful and general for the synthesis of symmetrical pyridines. In addition, more attentions were focused recently on the synthesis of unsymmetrical pyridines and various methodologies such as transition-metal-catalyzed reaction[13] and metal-free condensation reactions of amines with carbonyl compounds[14,15] have been established. Although a lot of methods for building the pyridine motif have been achieved, simple and effective methodologies for the synthesis of symmetrical and asymmetrical pyridines using easily accessible starting materials are still highly desirable.

α,β,γ,δ-Unsaturated compounds used as Michael acceptors remain a challenge due to the difficulty in simultaneously controlling the regioselectivity (1,2-, 1,4- as well as 1,6-addition).[16] Over the last few years, Hayashi and co-workers have established rhodium- and iridium-catalyzed protocols that selectively perform 1,6-addition on the 2,4-dien-1-ones.[17] Selective 1,6-additions have also been reported with Grignard reagents, trialkylaluminums, and arylboronic acids utilizing copper-, iron-, and palladium-based catalysts.[18] In contrast, Alexakis et al. employed Grignard reagents to selectively yield 1,4-adducts with copper-based catalysts.[19] Pullarkat developed an efficient palladium-catalyzed regioselective 1,4-conjugate addition of arylboronic acids to 2,4-dien-1-ones.[20] More recently, Fletcher and co-worker reported copper-catalyzed asymmetric 1,4-addition of alkylzirconium species to α,β,γ,δ-unsaturated dienones and ynenones.[21] In our continuing efforts on the synthesis of pyridine derivatives through annulation of readily available starting materials,[14,22] we attempted the Michael addition of linear α,β,γ,δ-unsaturated dienones using ammonium formate as a nucleophile without any additives. Interestingly, 1,4-adducts were not afforded. The formed 1,2- or 1,6-Michael addition intermediates were simultaneously cyclized to the pyridines. Herein, we reported a new transformation of α,β,γ,δ-unsaturated compounds with ammonium formate for the synthesis of asymmetrical 2,6-diarylpyridines in a metal-free system.

We initiated our investigation by choosing 1,5-diphenylpenta-2,4-dien-1-one (**1a**) as our model substrate. We examined the effect of ammonia sources, solvents, mole ratios of ammonia source to the substrate **1a**, and temperatures on the transformation. In the presence of 5 equivalents of ammonium chloride, **1a** was converted to 2,6-diphenylpyridine (**2a**) in 65% in toluene at 110 °C in 16 hours (Table 1, entry 1). Instead of ammonium chloride, an improved yield of **2a** was afforded when ammonium acetate was applied as

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the ammonia source into the reaction system (entry 2). To our delight, the yield of **2a** could be increased to 85% when the reaction was carried out with ammonium formate (entry 3). In contrast, the reaction failed when ammonia or methylamine solution was applied as the ammonia source. The effect of solvents on the reaction was then investigated. Apart from toluene, DMSO, DMF, and *N*,*N*-dimethylacetamide (DMAC) were examined and significantly lower yields were achieved compared to that with toluene (entries 6–8). Surprisingly, very low yield of **2a** was detected in xylene and chlorobenzene, respectively (entries 9 and 10). The influence of the amount of ammonium formate on the yield was also examined. It was found that only a trace amount of **2a** was afforded when the mole ratio of ammonium formate to **1a** was decreased to 1 (entry 11). When increasing the amount of ammonium formate to 3 equivalents, the yield of **2a** was increased to 28% (entry 12). Further increasing the amount of ammonium formate from 5 equivalents to 7 equivalents or more did not significantly improve the yield (entry 13 vs 3). In addition, the yield of the desired product was dramatically decreased with lower reaction temperatures (entries 14–16). On the other hand, increasing the reaction temperature to 130 °C did not improve the yield (entry 17). Based on these results, it was proposed that the optimal reaction conditions were **1a** (1 mmol) and ammonium formate (5 mmol) in toluene (3 mL) at 110 °C in an open air for 16 hours.

With the optimal reaction condition established, we progressed to explore the substrate scope of 1,5-diarylpenta-2,4-dien-1-ones in order to evaluate the reaction generality. The data are summarized in Scheme 1. We first proceeded to screen the substituent effect by variation of the aryl group at the carbonyl carbon (α-position). To test the effect of steric hindrance on the reaction output, both electron-donating groups (EDG, for example, Me and OMe) and electron-withdrawing groups (EWG, for example, F, Cl, and Br) at the *ortho*-, *meta*- and *para*-positions of the phenyl group at the carbonyl site of the 2,4-dien-1-ones **1** (**1b–f**,**g–k**,**m–q**) were introduced. It was found that the reaction exhibited satisfactory tolerance of the substrates containing either EDG or EWG. The average yields of product **2** containing EDG (Me and OMe) and EWG (F, Cl, and Br) are similar, indicating that the electronic nature of the aryl group on the 2,4-dien-1-ones had no significant influence on the yield. In contrast, the reaction of *ortho*-substituted **1** (**2b–f**) proceeded in lower yields compared with those of *meta*- and *para*-substituted analogues (**2g–k** and **2m–q**). The result demonstrates that the steric hindrance has appreciable influence on the product yield. In addition, the reaction of substrate containing an OH (**1l**) or NMe_2 (**1s**) group also proceeded smoothly but with moderate yields (38% and 36%, respectively). On the other hand, a strong electron-withdrawing nitro-substituted 2,4-dien-1-one (**1t**) was inefficient for the preparation of the desired product.

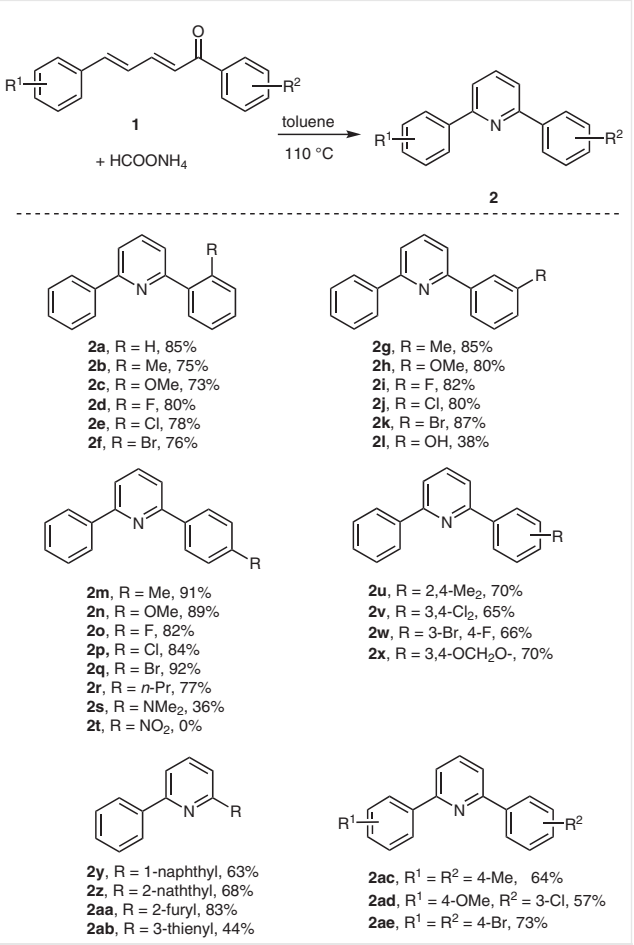
Table 1 Optimization of Reaction Conditions[a]

Entry	Solvent	Ammonia source (equiv)	Temp (°C)	Yield (%)
1	toluene	NH_4Cl (5)	110	65
2	toluene	NH_4OAc (5)	110	74
3	**toluene**	**$HCOONH_4$ (5)**	**110**	**85**, trace[b]
4	toluene	$NH_3{\cdot}H_2O$ (5)	110	0
5	toluene	$MeNH_2$ (5)	110	0
6	DMSO	$HCOONH_4$ (5)	110	62
7	DMF	$HCOONH_4$ (5)	110	42
8	DMAC	$HCOONH_4$ (5)	110	23
9	xylene	$HCOONH_4$ (5)	110	10
10	PhCl	$HCOONH_4$ (5)	110	trace
11	toluene	$HCOONH_4$ (1)	110	trace
12	toluene	$HCOONH_4$ (3)	110	28
13	toluene	$HCOONH_4$ (7)	110	87
14	toluene	$HCOONH_4$ (5)	20	0
15	toluene	$HCOONH_4$ (5)	70	40
16	toluene	$HCOONH_4$ (5)	90	75
17	toluene	$HCOONH_4$ (5)	130	84

[a] Reaction conditions: **1a** (1 mmol), ammonia source and solvent (3 mL) at the indicated reaction conditions for 16 h.
[b] Reaction under N_2 atmosphere.

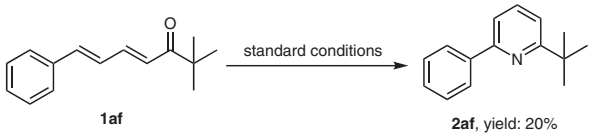
The reaction generality of disubstituted phenyl and heterocyclic 2,4-dien-1-ones was also investigated. In a similar fashion to monosubstituted analogues, the di-substituted phenyl 2,4-dien-1-ones (**1u–x**) were well tolerable for the transformation and the corresponding 2,6-diarylpyridines were afforded in moderate yields (65–70%). Compared to those of monosubstituted analogues, the yields for disubstituted 2,6-diarylpyridines are slightly lower. This can be clarified by the steric hindrance effect. When naphthyl and heterocyclic 2,4-dien-1-ones were employed, the transformation was also successful under the standard reaction conditions and the corresponding 2,6-disubstituted pyridines **2y–ab** were produced in moderate to good yields.

The scope of substituted phenyl group at δ-position of the 2,4-dien-1-ones in this novel reaction was also examined (Scheme 1). The 2,4-dien-1-ones bearing either EDG such as 4-Me and 4-OMe or EWG such as 4-Br at the δ-phenyl group, underwent the reaction smoothly to provide the corresponding 2,6-diarylpyridines **2ac–ae** in moderate to good yields.

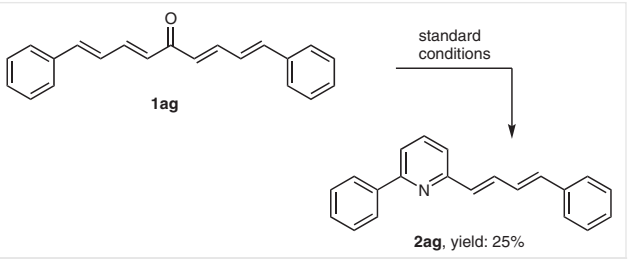


Scheme 1 Scope of the substrates. *Reagents and conditions*: **1** (1 mmol), $HCOONH_4$ (5 mmol), toluene (3 mL), 110 °C, 16 h. Isolated yields are shown.

In addition, several aliphatic linear α,β,γ,δ-unsaturated ketones such as γ-methyl, δ-ethyl, and α-methyl 2,4-dien-1-ones were attempted to investigate for the annulation reaction. However, only the aliphatic 2,4-dien-1-one on carbonyl carbon **1af** was successfully synthesized and only 20% yield of the desired product **2af** was achieved for this cycloaddition under the standard conditions (Equation 1). Furthermore, 1,9-diphenylnona-1,3-6,8-tetraen-5-one (**1ag**), which was synthesized from cinnamaldehyde and acetone under basic conditions (NaOH/EtOH), was found to be converted to the corresponding product **2ag** in a moderate yield (Equation 2).

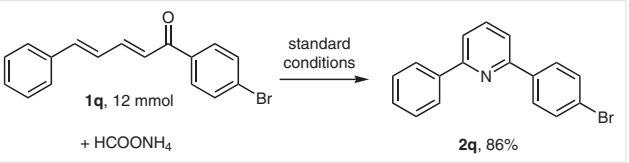


Equation 1 Synthesis of 2-(*tert*-butyl)-6-phenylpyridine (**2af**)



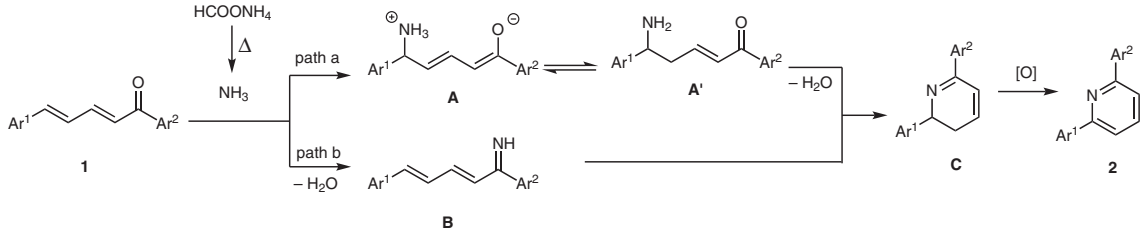
Equation 2 Synthesis of 2-phenyl-6-(4-phenylbuta-1,3-dien-1-yl)pyridine (**2ag**)

In order to demonstrate the suitability of this new synthetic method on an enlarged scale, a scale-up experiment (12 mmol) was carried out to prepare **2q**. The reaction of the starting material **1q** and ammonium formate under standard conditions proceeded smoothly to afford the corresponding product **2q** in 86% yield (Scheme 2) without a significant loss of efficiency (1 mmol scale, 92%).



Scheme 2 Gram-scale synthesis of **2q**

Based on the results of our experiments, a plausible mechanism for the reaction is proposed (Scheme 3). Initially, at high temperature conditions, the thermal decomposition of ammonium formate produces ammonia source. The electrophilicity of the 2,4-dien-1-one **1** allows it to react with the resulting ammonia source. As 1,4-adducts were not observed, nucleophilic attack at the β-position of 2,4-dien-1-one is ruled out, leaving two other possibilities, namely 1,6- (path a) and 1,2-addition (path b). The resulting intermediate **A** or its tautomeric form **A′** from path a performs an annulation by nucleophilic attack of amine on the carbonyl group followed by elimination of one molecule of water to afford intermediate **C**. Intermediate **C** can also be produced from intermediate **B**, where the nitrogen of imine attacks the δ-C to form a six-membered ring. In the presence of oxygen, the 2,3-dihydropyridine **C** is readily oxidized to lead to the formation of final product **2**. In fact, oxygen is necessary for the transformation, as the desired product failed to be formed under nitrogen atmosphere (Table 1, entry 3).



Scheme 3 Proposed mechanism

In summary, a simple and efficient method for the Michael addition of 1,5-diarylpenta-2,4-dien-1-ones **1** with an ammonium source has been developed for the synthesis of 2,6-diarylpyridines **2**. The method has the advantages of toleration of a wide range of substituents, operational simplicity, no additives, high yields, high regioselectivity, and readily available starting materials. This method can be readily extended to a large scale and has potential to be applied to industrial synthesis.

All reagents and solvents were used from commercial sources, unless otherwise stated. All raw materials are obtained from commercial sources or synthesized and used as such. All experiments were conducted in the air. Precoated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were used for TLC. Column chromatography was carried out on silica gel (240–400 mesh) with petroleum ether (PE) and EtOAc as eluent. The ^{1}H and ^{13}C NMR spectra of the 200/400/600 MHz and 50/100/125 MHz NMR spectrometers were recorded in $CDCl_3$/DMSO-d_6, respectively. Chemical shifts are reported as δ peaks. Melting points are uncorrected. Mass spectra were obtained using an LC-MS (ESI) mass or GC-MS mass spectrometer.

2,6-Diarylpyridines; 2,6-Diphenylpyridine (2a); Typical Procedure

1,5-Diphenylpenta-2,4-dien-1-one (**1a**; 234 mg, 1 mmol) and $HCOONH_4$ (315 mg, 5 mmol) were added to a solution of toluene (3.0 mL), and the reaction mixture was stirred in a tube at 110 °C for 16 h. The reaction was monitored by TLC. Once the reaction was complete, the mixture was treated with H_2O (15.0 mL) and EtOAc (8.0 mL). The organic and aqueous layers were then separated, and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the remaining residue was purified by column chromatography; yield: 196 mg (85%); white solid; mp 95–96 °C (Lit.[23] mp 81–82 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26–8.20 (m, 4 H), 7.88 (dd, *J* = 8.5, 7.1 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 2 H), 7.60–7.55 (m, 4 H), 7.53–7.48 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.87, 139.51, 137.53, 129.02, 128.72, 127.04, 118.68.

EI-MS: *m*/*z* = 232 $[M + H]^+$.

2-Phenyl-6-(*o*-tolyl)pyridine (2b)[23]

White solid; yield: 184 mg (75%); mp 61–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.80 (t, *J* = 7.8 Hz, 1 H), 7.69 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.50–7.44 (m, 3 H), 7.43–7.39 (m, 1 H), 7.35 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.31 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.81, 156.50, 140.52, 139.47, 136.96, 136.12, 130.88, 129.80, 128.88, 128.66, 128.26, 127.01, 125.87, 122.39, 118.20, 20.70.

EI-MS: *m*/*z* = 246 $[M + H]^+$.

2-(2-Methoxyphenyl)-6-phenylpyridine (2c)[23]

Pale yellow oil; yield: 191 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.1, 1.5 Hz, 2 H), 8.01 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.82 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.64 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.49–7.44 (m, 2 H), 7.42–7.35 (m, 2 H), 7.11 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.00 (dd, *J* = 8.3, 1.1 Hz, 1 H), 3.87 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.24, 156.80, 155.50, 139.77, 136.37, 131.52, 129.94, 129.29, 128.77, 128.65, 127.01, 123.56, 121.11, 118.35, 111.48, 55.67.

EI-MS: *m*/*z* = 262 $[M + H]^+$.

2-(2-Fluorophenyl)-6-phenylpyridine (2d)

Pale yellow oil; yield: 199 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (td, *J* = 7.9, 1.9 Hz, 1 H), 8.03–7.98 (m, 2 H), 7.68–7.62 (m, 2 H), 7.56 (dd, *J* = 6.3, 2.5 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.32–7.28 (m, 1 H), 7.25 (ddd, *J* = 8.1, 5.1, 2.0 Hz, 1 H), 7.19–7.15 (m, 1 H), 7.05 (ddd, *J* = 11.5, 8.1, 1.3 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.83 (d, *J* = 249.8 Hz), 157.04, 152.85, 139.39, 137.20, 131.33 (d, *J* = 3.0 Hz), 130.36, 130.45, 129.06, 128.76, 127.00, 124.51 (d, *J* = 3.5 Hz), 122.93, 119.01, 116.22 (d, *J* = 23.2 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}FN$ $[M + H]^+$: 250.1027; found: 250.1033.

2-(2-Chlorophenyl)-6-phenylpyridine (2e)[23]

Pale yellow oil; yield: 207 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.05 (m, 2 H), 7.78 (t, *J* = 7.8 Hz, 1 H), 7.70 (ddd, *J* = 7.9, 4.8, 1.5 Hz, 2 H), 7.58 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.49–7.43 (m, 3 H), 7.41–7.38 (m, 1 H), 7.37–7.29 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.13, 156.60, 139.46, 139.38, 136.68, 132.37, 131.92, 130.25, 129.59, 129.06, 128.78, 127.12, 127.04, 123.18, 119.11.

EI-MS: *m*/*z* = 266 $[M + H]^+$.

2-(2-Bromophenyl)-6-phenylpyridine (2f)[24]

Pale yellow oil; yield: 235 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H), 7.79 (t, *J* = 7.8 Hz, 1 H), 7.69 (td, *J* = 7.8, 1.1 Hz, 2 H), 7.62 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.52 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.49–7.43 (m, 2 H), 7.42–7.37 (m, 2 H), 7.26–7.22 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.05, 157.00, 141.45, 139.36, 136.69, 133.46, 131.76, 129.71, 129.04, 128.76, 127.56, 127.15, 122.99, 121.99, 119.13.

EI-MS: *m*/*z* = 310 $[M + H]^+$.

2-Phenyl-6-(*m*-tolyl)pyridine (2g)

White solid; mp 60–61 °C; yield: 207 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.12 (m, 2 H), 7.97 (d, *J* = 1.8 Hz, 1 H), 7.92 (d, *J* = 7.7 Hz, 1 H), 7.79 (dd, *J* = 8.4, 7.2 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 2 H), 7.50 (dd, *J* = 8.2, 6.6 Hz, 2 H), 7.46–7.35 (m, 2 H), 7.25 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.02, 156.81, 139.54, 139.44, 138.29, 137.42, 129.74, 128.94, 128.67, 128.58, 127.70, 127.01, 124.12, 118.75, 118.61, 21.62.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}N$ $[M + H]^+$: 245.1204; found: 245.1212.

2-(3-Methoxyphenyl)-6-phenylpyridine (2h)

White solid; yield: 209 mg (80%); mp 82–83 °C (Lit.[23] mp 83–85 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.1, 1.8 Hz, 2 H), 7.83–7.75 (m, 2 H), 7.71–7.66 (m, 3 H), 7.53–7.47 (m, 2 H), 7.45–7.38 (m, 2 H), 6.98 (dd, *J* = 8.2, 2.5 Hz, 1 H), 3.91 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.01, 156.74, 156.54, 140.98, 139.40, 137.47, 129.66, 128.98, 128.68, 126.97, 119.40, 118.79, 114.58, 112.54, 55.38.

EI-MS: *m*/*z* = 262 $[M + H]^+$.

2-(3-Fluorophenyl)-6-phenylpyridine (2i)

Pale yellow oil; yield: 204 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.12 (m, 3 H), 8.00 (dt, *J* = 7.0, 1.9 Hz, 1 H), 7.82 (t, *J* = 7.8 Hz, 1 H), 7.71 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.53–7.48 (m, 2 H), 7.46–7.43 (m, 1 H), 7.42–7.39 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.04, 155.34, 141.29, 139.21, 137.69, 134.82, 129.94, 129.18, 128.97, 128.78, 127.18, 127.02, 125.04, 119.25, 118.71.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}FN$ $[M + H]^+$: 250.1027; found: 250.1033.

2-(3-Chlorophenyl)-6-phenylpyridine (2j)

Pale yellow oil; yield: 212 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.11 (m, 3 H), 7.99 (dt, *J* = 6.8, 1.9 Hz, 1 H), 7.80 (t, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 6.9 Hz, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 2 H), 7.45–7.38 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.04, 155.34, 141.30, 139.22, 137.68, 134.82, 129.93, 129.18, 128.96, 128.78, 127.19, 127.02, 125.04, 119.24, 118.70.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}ClN$ $[M + H]^+$: 266.0731; found: 266.0733.

2-(3-Bromophenyl)-6-phenylpyridine (2k)

Pale yellow oil; yield: 269 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (t, *J* = 2.0 Hz, 1 H), 8.14–8.08 (m, 2 H), 8.01 (dt, *J* = 7.8, 1.4 Hz, 1 H), 7.76 (t, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.59 (d, *J* = 7.7 Hz, 1 H), 7.54–7.46 (m, 3 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.01, 155.19, 141.55, 139.21, 137.70, 131.91, 130.26, 130.11, 129.22, 128.81, 127.05, 125.54, 123.09, 119.27, 118.72.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}BrN$ $[M + H]^+$: 310.0226; found: 310.0218.

3-(6-Phenylpyridin-2-yl)phenol (2l)

Pale yellow oil; yield: 94 mg (38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 2.3 Hz, 1 H), 7.98–7.94 (m, 2 H), 7.65 (d, *J* = 8.1 Hz, 1 H), 7.54 (dd, *J* = 8.1, 2.3 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.23 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.45, 149.91, 139.90, 139.15, 137.25, 135.00, 128.89, 128.80, 128.75, 128.73, 126.79, 126.52, 120.38.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}NO$ $[M + H]^+$: 248.1070; found: 248.1077.

2-Phenyl-6-(*p*-tolyl)pyridine (2m)

White solid; yield: 223 mg (91%); mp 92–93 °C (Lit.[25] mp 91–92 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.19 (m, 2 H), 8.11 (d, *J* = 8.2 Hz, 2 H), 7.88–7.83 (m, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.56 (t, *J* = 7.4 Hz, 2 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.36 (d, *J* = 7.7 Hz, 2 H), 2.48 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.85, 156.73, 139.45, 139.06, 137.55, 136.58, 129.45, 129.00, 128.70, 127.08, 126.95, 118.45, 21.34.

EI-MS: *m*/*z* = 246 $[M + H]^+$.

2-(4-Methoxyphenyl)-6-phenylpyridine (2n)

White solid; yield: 232 mg (89%); mp 131–133 °C (Lit.[25] mp 132–133 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (td, *J* = 8.8, 1.8 Hz, 4 H), 7.84 (t, *J* = 7.8 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 2 H), 7.55 (t, *J* = 7.4 Hz, 2 H), 7.48 (t, *J* = 7.3 Hz, 1 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 3.93 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.61, 156.65, 156.47, 139.38, 137.63, 131.91, 129.04, 128.71, 128.40, 127.10, 118.13, 118.07, 114.10, 55.41.

EI-MS: *m*/*z* = 262 $[M + H]^+$.

2-(4-Fluorophenyl)-6-phenylpyridine (2o)

Yellow solid; yield: 204 mg (82%); mp 94–95 °C (Lit.[23] mp 94–95 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.09 (m, 4 H), 7.85–7.75 (m, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.50 (td, *J* = 7.8, 7.3, 1.7 Hz, 2 H), 7.44 (td, *J* = 7.1, 1.6 Hz, 1 H), 7.18 (td, *J* = 8.6, 1.5 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.59 (d, *J* = 248.2 Hz), 156.35 (d, *J* = 107.7 Hz), 139.36, 137.62, 135.64, 129.09, 128.84, 128.74, 126.99, 118.61, 118.31, 115.71, 115.49.

EI-MS: *m*/*z* = 250 $[M + H]^+$.

2-(4-Chlorophenyl)-6-phenylpyridine (2p)[23]

White solid; yield: 223 mg (84%); mp 106–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.07 (m, 4 H), 7.81 (t, *J* = 7.8 Hz, 1 H), 7.70 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.66 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.53–7.41 (m, 5 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.94, 155.57, 139.25, 137.86, 137.62, 135.06, 129.10, 128.85, 128.72, 128.24, 126.96, 118.91, 118.39.

EI-MS: *m*/*z* = 266 $[M + H]^+$.

2-(4-Bromophenyl)-6-phenylpyridine (2q)

White solid; yield: 284 mg (92%); mp 115–116 °C (Lit.[25] mp 110–111 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.10 (m, 2 H), 8.05–8.00 (m, 2 H), 7.81 (t, *J* = 7.8 Hz, 1 H), 7.70 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.65 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.63–7.59 (m, 2 H), 7.53–7.48 (m, 2 H), 7.46–7.41 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.99, 155.64, 139.27, 138.35, 137.66, 131.83, 129.15, 128.76, 128.57, 126.99, 123.45, 119.00, 118.39.

EI-MS: *m*/*z* = 310 $[M + H]^+$.

2-Phenyl-6-(4-propylphenyl)pyridine (2r)

Pale yellow oil; yield: 210 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.13 (m, 2 H), 8.06 (d, *J* = 8.2 Hz, 2 H), 7.82–7.76 (m, 1 H), 7.66 (d, *J* = 8.3 Hz, 2 H), 7.49 (dd, *J* = 8.2, 6.5 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 2.67–2.63 (m, 2 H), 1.72–1.66 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.94, 156.74, 143.77, 139.60, 137.41, 137.01, 128.92, 128.86, 128.67, 127.00, 126.89, 118.41, 118.33, 37.86, 24.55, 13.86.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}N$ $[M + H]^+$: 274.1590; found: 274.1590.

***N*,*N*-Dimethyl-4-(6-phenylpyridin-2-yl)aniline (2s)**

White solid; yield: 99 mg (36%); mp 175–178 °C (Lit.[23] mp 176–178 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 8.3, 1.3 Hz, 2 H), 8.10–8.05 (m, 2 H), 7.74 (t, *J* = 7.8 Hz, 1 H), 7.59 (ddd, *J* = 13.9, 7.8, 0.9 Hz, 2 H), 7.50–7.46 (m, 2 H), 7.42 (d, *J* = 7.4 Hz, 1 H), 6.86–6.80 (m, 2 H), 3.04 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.47, 149.40, 139.87, 137.21, 135.26, 128.90, 128.61, 127.87, 126.99, 126.59, 120.63, 117.21, 112.42, 40.58.

EI-MS: *m*/*z* = 275 $[M + H]^+$.

2-(2,4-Dimethylphenyl)-6-phenylpyridine (2u)

Pale yellow oil; yield: 181 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.1 Hz, 2 H), 7.78 (t, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.46 (t, *J* = 7.3 Hz, 2 H), 7.40 (dd, *J* = 7.5, 1.9 Hz, 2 H), 7.34 (d, *J* = 7.7 Hz, 1 H), 7.14–7.09 (m, 2 H), 2.46 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.88, 156.43, 139.58, 138.05, 137.81, 136.92, 135.99, 131.72, 129.85, 128.88, 128.68, 127.04, 126.63, 122.37, 117.97, 21.20, 20.71.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}N$ $[M + H]^+$: 260.1434; found: 260.1439.

2-(3,4-Dichlorophenyl)-6-phenylpyridine (2v)

Pale yellow oil; yield: 194 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 2.1 Hz, 1 H), 8.15–8.08 (m, 2 H), 7.96 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.72 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.64 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.61–7.55 (m, 1 H), 7.54–7.49 (m, 2 H), 7.47–7.42 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.15, 154.32, 139.39, 139.05, 137.78, 133.08, 132.99, 130.62, 129.27, 128.87, 128.80, 127.00, 126.04, 119.43, 118.46.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}ClN$ $[M + H]^+$: 300.0341; found: 300.0348.

2-(3-Bromo-4-fluorophenyl)-6-phenylpyridine (2w)

Pale yellow oil; yield: 216 mg (66%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.53 (dd, *J* = 6.8, 2.2 Hz, 1 H), 8.28 (ddd, *J* = 8.8, 4.9, 2.5 Hz, 1 H), 8.20 (dd, *J* = 7.3, 1.7 Hz, 2 H), 8.00–7.96 (m, 2 H), 7.57–7.52 (m, 3 H), 7.49 (dq, *J* = 8.3, 3.0 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 159.38 (d, *J* = 247.3 Hz), 156.24, 153.61, 139.03, 138.88, 137.19, 131.88, 129.75, 129.30, 128.52, 128.44, 127.12, 119.67 (d, *J* = 36.8 Hz), 117.52 (d, *J* = 22.4 Hz), 109.14 (d, *J* = 21.2 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}BrFN$ $[M + H]^+$: 328.0132; found: 328.0123.

2-(Benzo[*d*][1,3]dioxol-5-yl)-6-phenylpyridine (2x)

White solid; yield: 193 mg (70%); mp 92–93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.0, 1.5 Hz, 2 H), 7.78 (t, *J* = 7.8 Hz, 1 H), 7.72 (d, *J* = 1.8 Hz, 1 H), 7.64 (ddd, *J* = 8.1, 3.3, 1.3 Hz, 2 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 2 H), 7.42 (t, *J* = 7.3 Hz, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 6.03 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.65, 156.26, 148.47, 148.26, 139.46, 137.47, 134.02, 128.98, 128.69, 126.97, 120.96, 118.20, 118.06, 108.39, 107.51, 101.30.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{14}NO_2$ $[M + H]^+$: 276.1019; found: 276.1023.

2-(Naphthalen-1-yl)-6-phenylpyridine (2y)[23]

Pale yellow oil; yield: 177 mg (63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.11 (m, 1 H), 7.99 (d, *J* = 7.3 Hz, 2 H), 7.78 (d, *J* = 9.0 Hz, 2 H), 7.69 (t, *J* = 7.7 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.56 (dd, *J* = 7.1, 1.2 Hz, 1 H), 7.45–7.41 (m, 1 H), 7.38–7.31 (m, 5 H), 7.30–7.27 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.09, 156.93, 139.46, 138.83, 137.25, 134.11, 131.38, 129.06, 128.98, 128.80, 128.43, 127.70, 127.16, 126.43, 126.01, 125.91, 125.41, 123.49, 118.66.

EI-MS: *m*/*z* = 282 $[M + H]^+$.

2-(Naphthalen-2-yl)-6-phenylpyridine (2z)[24]

Yellow solid; yield: 191 mg (68%); mp 101–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 8.33 (dd, *J* = 8.6, 1.8 Hz, 1 H), 8.22–8.18 (m, 2 H), 7.97 (t, *J* = 7.8 Hz, 2 H), 7.91–7.83 (m, 3 H), 7.72 (dd, *J* = 5.8, 2.9 Hz, 1 H), 7.55–7.49 (m, 4 H), 7.45 (t, *J* = 7.3 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.97, 156.71, 139.49, 137.56, 136.77, 133.71, 133.50, 129.03, 128.75, 128.72, 128.34, 127.68, 127.05, 126.47, 126.33, 126.23, 124.75, 118.94, 118.76.

EI-MS: *m*/*z* = 282 $[M + H]^+$.

2-(Furan-2-yl)-6-phenylpyridine (2aa)

Pale yellow oil; yield: 183 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.05 (m, 2 H), 7.77 (t, *J* = 7.8 Hz, 1 H), 7.62 (ddd, *J* = 14.2, 7.9, 1.0 Hz, 2 H), 7.54 (dd, *J* = 1.8, 0.9 Hz, 1 H), 7.51–7.46 (m, 2 H), 7.45–7.39 (m, 1 H), 7.20 (dd, *J* = 3.4, 0.9 Hz, 1 H), 6.55 (dd, *J* = 3.4, 1.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.99, 154.11, 149.24, 143.21, 139.25, 137.37, 129.05, 128.71, 127.00, 118.60, 116.80, 112.05, 108.78.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}NO$ [M + H]$^+$: 222.0913; found: 222.0920.

2-Phenyl-6-(thiophen-3-yl)pyridine (2ab)[23]

Yellow solid; yield: 104 mg (44%); mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.10 (m, 1 H), 8.03 (ddd, *J* = 11.6, 3.0, 1.3 Hz, 1 H), 7.82–7.74 (m, 2 H), 7.70 (s, 1 H), 7.64–7.56 (m, 1 H), 7.54–7.46 (m, 2 H), 7.45–7.39 (m, 2 H), 7.32 (d, *J* = 0.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.84, 153.66, 142.46, 137.47, 129.01, 128.70, 127.14, 126.98, 126.51, 126.15, 123.67, 118.53, 116.65.

EI-MS: *m*/*z* = 238 [M + H]$^+$.

2,6-Di-*p*-tolylpyridine (2ac)

White solid; yield: 166 mg (64%); mp 157–159 °C (Lit.[23] mp 157–159 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 4 H), 7.75 (dd, *J* = 8.4, 7.2 Hz, 1 H), 7.62 (d, *J* = 7.7 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 4 H), 2.41 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.75, 138.90, 137.35, 136.83, 129.41, 126.88, 118.06, 21.35.

EI-MS: *m*/*z* = 260 [M + H]$^+$.

2-(3-Chlorophenyl)-6-(4-methoxyphenyl)pyridine (2ad)

White solid; yield: 168 mg (57%); mp 155–157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.15 (m, 1 H), 8.10 (d, *J* = 8.9 Hz, 2 H), 7.99 (dt, *J* = 7.0, 1.9 Hz, 1 H), 7.78 (t, *J* = 7.8 Hz, 1 H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.60 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.43–7.39 (m, 2 H), 7.02 (d, *J* = 8.9 Hz, 2 H), 3.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.62, 156.68, 155.17, 141.40, 137.59, 134.78, 131.84, 129.89, 128.87, 128.29, 127.16, 125.00, 118.47, 117.99, 114.12, 55.40.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}ClNO$ [M + H]$^+$: 296.0837; found: 296.0839.

2,6-Bis(4-bromophenyl)pyridine (2ae)

White solid; yield: 283 mg (73%); mp 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.6 Hz, 4 H), 7.81 (dd, *J* = 8.3, 7.3 Hz, 1 H), 7.67 (d, *J* = 7.7 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.79, 138.12, 137.81, 131.88, 128.53, 123.61, 118.72.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}BrN$ [M + H]$^+$: 387.9331; found: 387.9336.

2-(*tert*-Butyl)-6-phenylpyridine (2af)

Pale yellow oil; yield: 42 mg (20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.07 (m, 2 H), 7.66 (t, *J* = 7.8 Hz, 1 H), 7.54 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.46 (t, *J* = 7.3 Hz, 2 H), 7.41–7.36 (m, 1 H), 7.28–7.25 (m, 1 H), 1.43 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.97, 155.37, 139.92, 136.76, 128.64, 128.58, 126.85, 117.35, 116.86, 30.25, 29.73.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}N$ [M + H]$^+$: 212.1434; found: 212.1431.

2-Phenyl-6-(4-phenylbuta-1,3-dien-1-yl)pyridine (2ag)

Pale yellow oil; yield: 71 mg (25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.6 Hz, 2 H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.65–7.60 (m, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 7.52–7.41 (m, 5 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.28 (s, 1 H), 7.23 (s, 1 H), 7.09–6.99 (m, 1 H), 6.88–6.77 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.06, 155.36, 139.54, 137.18, 137.16, 135.22, 133.39, 132.22, 128.98, 128.72, 128.66, 127.94, 127.06, 127.02, 126.65, 120.51, 118.78.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{18}N$ [M + H]$^+$: 284.1434; found: 284.1438.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610725.

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