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Direct synthesis of 2-methylpyridines via I_2-triggered [3 + 2 + 1] annulation of aryl methyl ketoxime acetates with triethylamine as the carbon source

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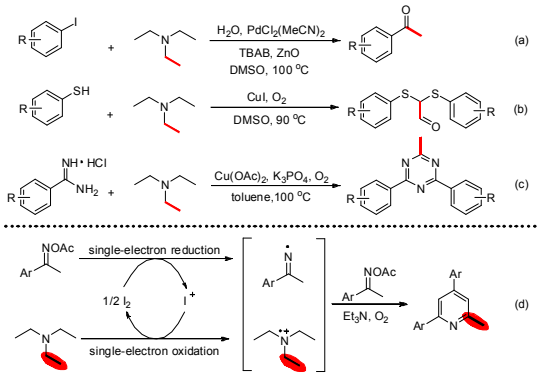
A facile and efficient [3 + 2 + 1] annulation of aryl methyl ketoxime acetates and triethylamine for the synthesis of 2-methylpyridines was disclosed. This reaction demonstrated that I_2 was effective to trigger N-O bond cleavage of oxime acetates generating of imine radicals. It was noteworthy that this transformation employed triethylamine as the carbon source for the direct formation of pyridines and introduction of methyl groups.

Introduction

The so-called "magic methyl effect" makes 2-methylpyridines very popular in many biologically active compounds, pharmaceuticals, and agrochemicals.[1] Meanwhile, 2-methylpyridines are also employed as a class of fascinating intermediates in organic and medicinal chemistry.[2] Consequently, continued effort has been devoted to exploring new and efficient strategies for the preparation of 2-methylpyridine backbones. Recently, the C2-methylation reactions of pyridine *N*-oxides involving a nucleophilic addition/elimination mechanism by employing Tebbe's reagent, Grignard reagent, or diborylmethane as the methyl sources have been reported by Nicolaou,[3] Larionov,[4] and Cho,[5] respectively. Macmillan and co-workers discovered the direct installation of the methyl group in pyridine with methanol by a photoredox-induced radical reaction, although inseparable regioisomeric mixtures were formed in some cases.[6] Moreover, as an alternative, the introduction of methyl group along with the construction of pyridine in one step would be beneficial for the selectivity and diversity of the final product.[7] Herein, we report a facile and efficient synthesis of 2-methylpyridines from aryl methyl ketoxime acetates with triethylamine (TEA) as the carbon source.

Recently, cleaving the highly stable C-N bond in TEA and applying the fragments to construct new C-N or C-C bonds have aroused much attention.[8] Whereas, compared to the extensive studies of TEA as amino sources via oxidative activation of C-N bond, its usage as carbon sources has rarely been explored and represents an important area in need of development. The Li group disclosed the first example of using Et_3N as the carbonyl source for constructing aryl methyl ketone skeletons by palladium-catalyzed oxidative coupling of aryl iodides with Et_3N and water (Scheme 1a).[9] Late on, Pan established a copper-catalyzed direct and selective β-sulfenylation of Et_3N through a radical pathway, providing a series of α,α-disulfenylated aldehydes (Scheme 1b).[10] Jiang et al. described a facile synthesis of 2-methyl-1,3,5-triazines via aerobic copper-catalyzed cyclization of amidines, which was a pioneering example of Et_3N serving as the carbon source to furnish heterocycles (Scheme 1c).[11] Among these transformations, single-electron oxidation of Et_3N generating the higher levels of reactivity of the iminium ion intermediate in situ was a basic process. In this paper, based on our recent study on I_2-triggered reductive cleavage of the N-O bond,[12] we demonstrate a metal-free coulping reaction of ketoxime acetate with the α-C(sp^3)-H bond of TEA via convergent integration of single-electron reduction and single-electron oxidation (Scheme 1d).

Scheme 1. TEA as the Carbon Sources via Oxidative Activation of C-N Bond



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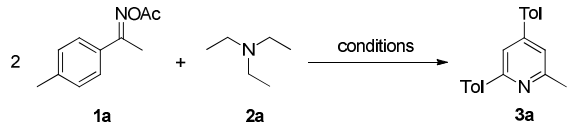
Results and discussion

Initially, the reaction of 4-methylacetophenone oxime acetate (**1a**) with TEA (**2a**) was chosen as the model reaction using 1.5 equiv of I_2 in toluene at 120 °C (Table 1). To our delight, the methyl-containing pyridine (**3a**) was obtained albeit in moderate yield (entry 1). This reaction indicated that cleavage of N-O bond in oxime acetates and C-N bond in TEA occurred in the presence of I_2. Subsequently, oxidants including O_2, TBHP (*tert*-butyl hydroperoxide), DTBP (di-*tert*-butyl peroxide), BPO (benzoyl peroxide), or H_2O_2 were added into the reaction system respectively, and we found dioxygen worked most efficiently (entries 2–6). However, only 36% of **3a** was obtained under a nitrogen atmosphere (entry 7). On the other hand, investigation into the effect of the loading of I_2 disclosed that reducing the amount of I_2 was negative to the results (entries 9–11). Next, various solvents such as 1,4-dioxane, CH_3CN, NMP (*N*-methyl-2-pyrrolidinone), DMSO, DCE, chlorobenzene, and DMF were screened (entries 12–18), revealing that toluene was found to be still the most suitable solvent for this transformation. Surprisingly, the yield of **3a** was improved to 72% on vigorous refluxing of the reaction mixture in a 140 °C oil bath (entry 20). By replacing I_2 with NIS or NH_4I, the desired product was isolated in 63% and 67% yields, respectively (entries 22–23). However, no methylation product was obtained in the presence of CuI, KI, or TBAI (entries 24–26), and no reaction occurred in the absence of iodine reagents, indicating that I_2 is essential for the reaction (entry 27). Moreover, varying the amount of TEA resulted in reducing the reaction efficiency (entries 28–29).

Table 1. Optimization of Reaction Conditions[a]

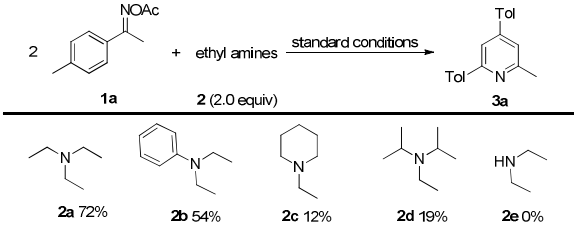


Entry	[I] (equiv)	Oxidant	Solvent	Temp. (°C)	Yield (%)[b]
1	I_2 (1.5)		toluene	120	40
2	I_2 (1.5)	O_2	toluene	120	61
3	I_2 (1.5)	TBHP	toluene	120	trace
4	I_2 (1.5)	DTBP	toluene	120	48
5	I_2 (1.5)	BPO	toluene	120	n.d.
6	I_2 (1.5)	H_2O_2	toluene	120	n.d.
7	I_2 (1.5)	Ar	toluene	120	36
8	I_2 (2.0)	O_2	toluene	120	60
9	I_2 (1.0)	O_2	toluene	120	50
10	I_2 (0.5)	O_2	toluene	120	23
11	I_2 (0.2)	O_2	toluene	120	trace
12	I_2 (1.5)	O_2	dioxane	120	42
13	I_2 (1.5)	O_2	CH_3CN	120	51
14	I_2 (1.5)	O_2	NMP	120	trace
15	I_2 (1.5)	O_2	DMSO	120	n.d.
16	I_2 (1.5)	O_2	DCE	120	n.r.
17	I_2 (1.5)	O_2	PhCl	120	12
18	I_2 (1.5)	O_2	DMF	120	17
19	I_2 (1.5)	O_2	toluene	160	55
20	**I_2 (1.5)**	**O_2**	**toluene**	**140**	**72**
21	I_2 (1.5)	O_2	toluene	100	15
22	NIS (1.5)	O_2	toluene	140	63
23	NH_4I (1.5)	O_2	toluene	140	67
24	CuI (1.5)	O_2	toluene	140	n.d.
25	KI (1.5)	O_2	toluene	140	n.r.
26	TBAI (1.5)	O_2	toluene	140	n.r.
27		O_2	toluene	140	n.r.
28[c]	I_2 (1.5)	O_2	toluene	140	39
29[d]	I_2 (1.5)	O_2	toluene	140	17

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), I_2 (0.75 mmol), oxidant (1.0 mmol), solvent (2 mL). [b]Isolated yield; n.d. = no desired product; n.r. = no reaction. [c]**2a** (1.5 mmol). [d]**2a** (0.5 mmol).

To evaluate the potential of amines to function as both the carbon source and methylation reagent, other various tertiary and secondary ethyl amines were further subjected to the standard conditions optimized for **2a**. As shown in Table 2, even though *N*,*N*-diethylaniline (**2b**) could afford **3a** in 54% yield, other ethyl amines were ineffective. These results clearly illustrated that the choice of amines was crucial for this annulation process.

Table 2. Representative Ethyl Amines



With the optimized reaction conditions in hand, the generality and scope of this efficient I_2-triggered [3 + 2 + 1] annulation of ketoxime acetates and TEA for the introduction of methyl groups was explored. It was revealed that this reaction featureed wide substrate scope of the ketoxime acetates (Scheme 2). Aryl methyl ketone *O*-acetyloximes bearing both electron-neutral (e.g., 4-Me, 3-Me, 2-Me, 4-Et, 4-*t*-Bu, 4-H) and electron-donating (e.g., 4-OMe, 4-OEt, 3,4-OCH_2O) on the aromatic rings were converted to the corresponding 2-methylpyridines in moderate to good yields (57–84%; **3a**–**3i**). These results suggested the steric effect played a role in the reaction (**3a**, **3b**, and **3c**). Much to our satisfaction, the optimized conditions were mild enough to be compatible with a broad range of halogenated (e.g., 4-F, 4-Cl, 4-Br, 3,4-Cl_2) substrates (50–61%; **3j**–**3m**), providing enormous possibilities for further modification. Notably, the acetophenone oxime acetates with strongly electron-withdrawing groups 4-CF_3 and 3-NO_2 could be accessed through this route to generate the desired products in a slightly low yield (46–55%; **3n**–**3o**). When β-naphthyl methyl ketoxime acetate was used as the substrate, the expected product (**3p**) could be isolated in 47% yield. In addition, the

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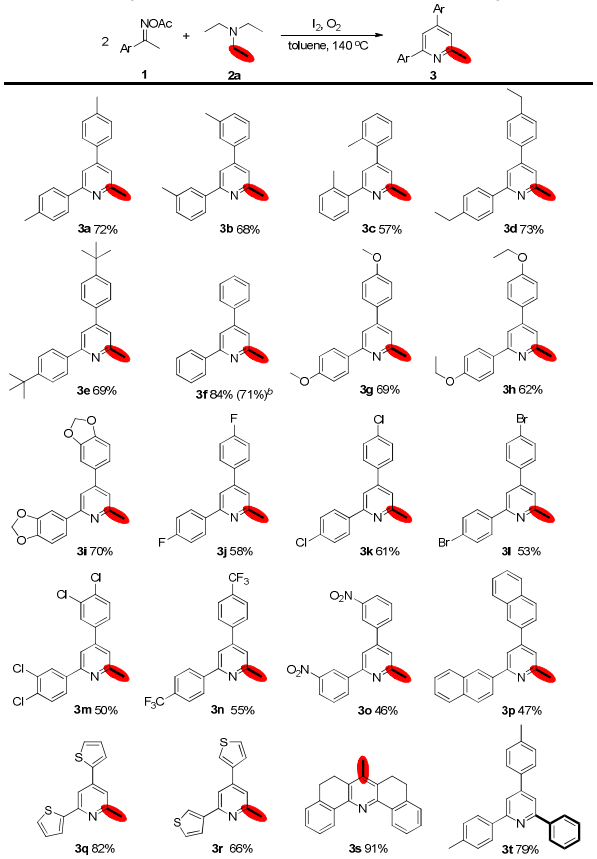
optimized conditions could be applied to thiophene-2-yl methyl ketoxime acetate and thiophene-3-yl methyl ketoxime acetate, delivering the annulation products in 82% and 66% yields, respectively (**3q**–**3r**). It is noteworthy that ketoxime acetate derived from α-tetralone underwent the desired reaction to afford the symmetrical 4-methylpyridine (**3s**) in excellent yield (91%). Unfortunately, no reaction took place when alkyl ketoxime acetates such as 3,3-dimethylbutan-2-one oxime acetates were employed as the substrate. Furthermore, tribenzylamine (**2f**) was also a good substrate for the reaction to form the desired 2-phenylpyridine (**3t**). However, no expected product was detected when *N*,*N*-dimethylaniline (**2g**), trimethylamine (25% in H_2O) (**2h**), or tripropylamine (**2i**) was submitted to the standard conditions. It is regrettable that this valuable tool did not install another alkyl onto the pyridine ring.

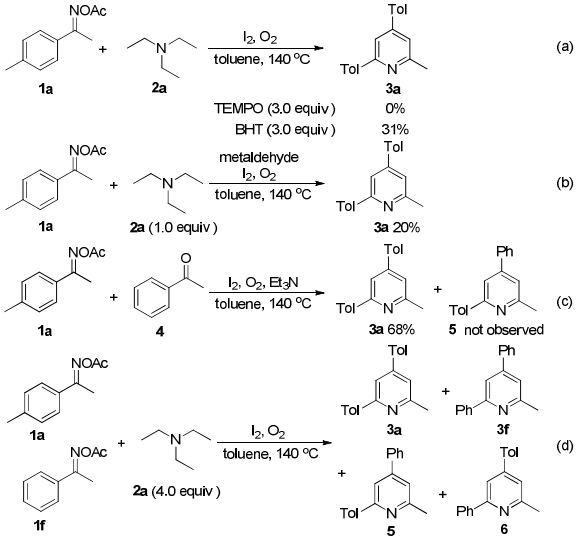
Scheme 2. Scope of Ketoxime Acetates and Tertiary Amines[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol) and I_2 (0.75 mmol) in toluene (2 mL) under oxygen balloon at 140 °C. Isolated yield. [b]Conducted on 10 mmol scale, isolated yield.

As we proposed above, this I_2-triggered coulping/cyclization might undergo radical process. Indeed, the inhibiton experiments of radical showed that TEMPO completely suppressed the reaction, and the yield of **3a** was reduced significantly in the presence of BHT (Scheme 3a). These results supported the proposed radical process via single electron transfer. The oxidation of TEA formed the iminium ion, which may generate in situ the acetaldehyde. However, when metaldehyde (3.0 equiv) instead of a part of TEA was subjected to this reaction system, a low yield of **3a** was obtained (Scheme 3b), which might be due to the higher levels of reactivity of the iminium ion intermediate in situ generated. When acetophenone was added to the reaction mixture, the **3a** was still obtained in 68% yield, but the pyridine (**5)** was not observed. This result demonstrated that the corresponding ketone was only the byproduct rather than the electrophile or intermediate in the reaction (Scheme 3c). In addition, we investigated the cross-coupling reaction between two representative substrates 4-methylacetophenone oxime acetate (**1a**) and acetophenone oxime acetate (**1f**) under standard conditions. Fortunately, all the products were successfully identified by HRMS analysis of the crude reaction extract (Scheme 3d).

Scheme 3. Control Experiments



We further experimented to develop a better understanding of the reaction mechanism by performing ^{13}C-labeling and D-labeling experiments under the optimized conditions using acetophenone-β,β,β-d_3 oxime acetate and acetophenone-β-^{13}C oxime acetate, respectively, as substrates. The corresponding desired products **3f'** and **3f-d_2** were obtained in 82% and 79% yields, respectively (Scheme 4a and 4b). These experimental results strongly suggested that methyl ketone *O*-acetyloximes provided four carbons to form the pyridine ring. Then, the speculation that the α-C of TEA was integrated into the final pyridines has been demonstrated when TEA-d_{15} was used in this reaction system (Scheme 4c). In addition, both of the deuterated experimental evidences are in agreement with the observation of internal D/H exchange in the 2-methylpyridines.

Scheme 4. ^{13}C-Labeling and D-Labeling Experiments

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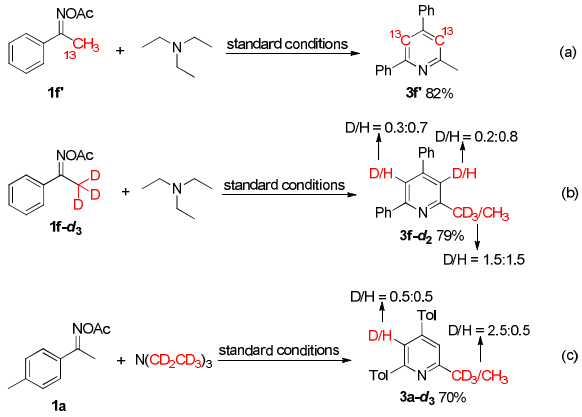
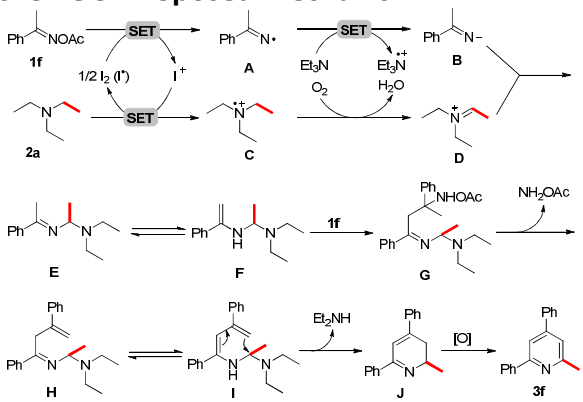


On the basis of the results in the current study and previous reports,[13] a possible mechanism has been proposed using acetophenone oxime acetate (**1f**) and TEA (**2a**) as examples (Scheme 5). Initially, the single-electron-transfer(SET) reduction of the N-O bond of oxime acetate **1f** with molecular iodine or iodine radical produced the hypervalent iodine species (I^+) and an iminyl radical intermediate **A**,[14] which was reductively quenched by Et_3N to produce the corresponding anion **B**.[15] Then, the imine-type intermediate **D** was formed from **2a** via a SET oxidative process.[16] Subsequently, the nucleophilic attack of **D** by intermediate **B** resulted in the formation of intermediate **E**. Next, the enamine intermediate **F** quickly generated from the tautomerization of **E** reacted with a second molecular of ketoxime acetate **1f** to give the intermediate **G** followed by the release of NH_2OAc to afford **H**. Finally, the intermediate **I** underwent sequential intramolecular deamination cyclization and oxidative aromatization reactions to provide the desired product **3f**.

Scheme 5. Proposed Mechanism



Conclusions

In summary, we have developed a facile and efficient I_2-triggered [3 + 2 + 1] annulation of aryl methyl ketoxime acetates and triethylamine to produce diverse 2-methylpyridines which are challenging to prepare by traditional methods. This strategy is based on convergent integration of single-electron reduction and single-electron oxidation for the N-O/C-N bond cleavages along with the sequential activation of Csp^3-H bond. Triethylamine performed as both the carbon source and electron donor in the reaction. Significantly, the method opens up a new strategy for I_2-induced transformation of oxime esters.

Experimental

General information

All substrates and reagents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). ^1H spectra were recorded in $CDCl_3$ on 400 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. ^{13}C spectra were recorded in $CDCl_3$ on 100 MHz NMR spectrometers and resonances (δ) are given in ppm. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source. Melting points were determined using XT-4 apparatus and not corrected.

General procedure for the synthesis of 3

A mixture of oxime acetates **1** (0.5 mmol), iodine (0.75 mmol), and Et_3N (1.0 mmol) in toluene (2 mL) was stirred under oxygen balloon at 140 °C. After disappearance of the reactant (monitored by TLC), and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and evaporation. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the product **3**.

2-methyl-4,6-di-*p*-tolylpyridine (3a):

Yield 72% (49.1 mg); pink solid; mp 91–94 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.33–7.24 (m, 5H), 2.67 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 157.5, 149.3, 138.8, 138.6, 137.1, 135.9, 129.7, 129.4, 127.0, 126.9, 119.3, 115.6, 24.8, 21.3, 21.2; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{19}NNa$: 296.1410; found: 296.1410.

2-methyl-4,6-di-*m*-tolylpyridine (3b):

Yield 68% (46.4 mg); brown oil; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.40–7.33 (m, 2H), 7.30 (s, 1H), 7.24 (t, J = 8.8 Hz, 2H), 2.69 (s, 3H), 2.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 157.8, 149.6, 139.8, 138.8, 138.7, 138.3, 129.6, 129.5, 128.9, 128.6, 127.8(4), 127.7(9), 124.2(4), 124.1(8), 119.7, 116.2, 24.8, 21.5(4), 21.4(9); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{20}N$: 274.1590; found: 274.1590.

2-methyl-4,6-di-*o*-tolylpyridine (3c):

Yield 57% (38.9 mg); red oil; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45–7.41 (m, 1H), 7.32–7.24 (m, 7H), 7.17 (s, 1H), 7.09 (s, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.2, 157.7, 150.1, 140.6, 139.5, 135.7, 135.0, 130.7, 130.6, 129.6, 129.3, 128.2, 128.1, 126.0, 125.9, 121.7(0), 121.6(5), 24.7, 20.3(7), 20.3(5); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{20}N$: 274.1590; found: 274.1590.

2,4-bis(4-ethylphenyl)-6-methylpyridine (3d):

Yield 73% (54.9 mg); pink oil; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.34–7.27 (m, 5H), 2.76–2.69 (m, 4H), 2.67 (s, 3H), 1.32–1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 157.6, 149.3, 145.2, 145.0,

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137.4, 136.2, 128.5, 128.2, 127.1, 127.0, 119.3, 115.7, 28.7, 28.6, 24.8, 15.6, 15.5; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{23}NNa$: 324.1723; found: 324.1724.

2,4-bis(4-(*tert*-butyl)phenyl)-6-methylpyridine (3e):

Yield 69% (61.6 mg); brown solid; mp 83–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, J = 8.4 Hz, 2H), 7.70 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.54–7.47 (m, 4H), 7.29 (s, 1H), 2.68 (s, 3H), 1.38 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 157.6, 152.1, 151.9, 149.2, 137.1, 135.9, 126.9, 126.7, 126.0, 125.6, 119.4, 115.8, 34.6(9), 34.6(5), 31.3(0), 31.2(9), 24.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{32}N$: 358.2529; found: 358.2527.

2-methyl-4,6-diphenylpyridine (3f):

Yield 84% (51.4 mg); pink solid; mp 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 (d, J = 7.2 Hz, 2H), 7.72 (s, 1H), 7.71–7.65 (m, 2H), 7.54–7.39 (m, 6H), 7.33 (s, 1H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.8, 157.7, 149.5, 139.8, 138.8, 129.0, 128.9, 128.8, 128.7, 127.1(4), 127.0(9), 119.8, 116.2, 24.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{16}N$: 246.1277; found: 246.1277.

2,4-bis(4-methoxyphenyl)-6-methylpyridine (3g):

Yield 69% (52.6 mg); yellow solid; mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 8.8 Hz, 2H), 7.64–7.58 (m, 3H), 7.21 (s, 1H), 6.99 (d, J = 8.8 Hz, 4H), 3.84 (s, 6H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.2(3), 160.2(1), 158.5, 157.1, 148.8, 132.5, 131.1, 128.3, 128.1, 118.6, 114.8, 114.3, 114.0, 55.2(9), 55.2(6), 24.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489; found: 306.1492.

2,4-bis(4-ethoxyphenyl)-6-methylpyridine (3h):

Yield 62% (51.6 mg); brown solid; mp 107–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 3H), 7.22 (s, 1H), 7.02–6.96 (m, 4H), 4.08 (q, J = 6.8 Hz, 4H), 2.65 (s, 3H), 1.48–1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6(8), 159.6(5), 158.4, 157.2, 148.9, 132.3, 130.9, 128.3, 128.1, 118.5, 114.9, 114.8, 114.6, 63.6, 63.5, 24.7, 14.7(9), 14.7(7); HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{24}NO_2$: 334.1802; found: 334.1806.

2,4-bis(benzo[*d*][1,3]dioxol-5-yl)-6-methylpyridine (3i):

Yield 70% (58.3 mg); yellow solid; mp 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56–7.50 (m, 3H), 7.21–7.12 (m, 3H), 6.93–6.87 (m, 2H), 6.02 (s, 2H), 6.00 (s, 2H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 157.0, 149.0, 148.4, 148.3(0), 148.2(6), 148.1, 134.3, 132.9, 121.0, 120.9, 119.0, 115.1, 108.7, 108.4, 107.6, 107.3, 101.4, 101.2, 24.74; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{16}NO_4$: 334.1074; found: 334.1073.

2,4-bis(4-fluorophenyl)-6-methylpyridine (3j):

Yield 58% (40.7 mg); pink solid; mp 95–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06–7.96 (m, 2H), 7.68–7.59 (m, 3H), 7.26 (s, 1H), 7.17 (q, J = 8.8 Hz, 4H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.7, 164.6, 162.2, 162.1, 159.0, 156.6, 148.6, 135.8, 134.8, 128.9, 128.8(4), 128.7(6) 119.6, 116.1, 115.9, 115.7, 115.6, 115.5, 24.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}F_2N$: 282.1089; found: 282.1088.

2,4-bis(4-chlorophenyl)-6-methylpyridine (3k):

Yield 61% (47.7 mg); white solid; mp 130–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.45 (t, J = 8.4 Hz, 4H), 7.28 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.2, 156.5, 148.4, 138.0, 137.1, 135.2, 135.0, 129.3, 128.9, 128.4, 128.3, 119.8, 115.6, 24.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}Cl_2N$: 314.0498; found: 314.0495.

2,4-bis(4-bromophenyl)-6-methylpyridine (3l):

Yield 53% (53.4 mg); light yellow solid; mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.8 Hz, 4H), 7.59 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.2, 156.5, 148.5, 138.4, 137.5, 132.2, 131.8, 128.7, 128.6, 123.4, 119.8, 115.5, 24.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}Br_2N$: 401.9488; found: 401.9486.

2,4-bis(3,4-dichlorophenyl)-6-methylpyridine (3m):

Yield 50% (47.9 mg); pink solid; mp 165–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16 (d, J = 1.6 Hz, 1H), 7.88 (dd, J = 8.4, 2.0 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.61 (s, 1H), 7.60–7.52 (m, 2H), 7.49 (dd, J = 8.4, 2.0 Hz, 1H), 7.29 (s, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5, 155.2, 147.5, 139.0, 138.3, 133.5, 133.4, 133.3, 133.0(5), 131.0(9), 130.7, 129.0, 128.9, 126.3, 126.2, 120.2, 115.5, 24.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{12}Cl_4N$: 381.9718; found: 381.9718.

2-methyl-4,6-bis(4-(trifluoromethyl)phenyl)pyridine (3n):

Yield 55% (52.4 mg); pink solid; mp 100–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16 (d, J = 8.0 Hz, 2H), 7.77 (s, 4H), 7.74 (d, J = 6.8 Hz, 3H), 7.37 (s, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 156.3, 148.4, 142.7, 142.1, 131.2, 131.0, 130.9, 130.7, 127.5, 127.4, 126.1(3), 126.0(9), 126.0(5), 126.0, 125.8, 125.7(1), 125.6(8), 125.6, 125.5, 125.3, 122.8, 122.6, 120.7, 116.4, 24.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{14}F_6N$: 382.1025; found: 382.1029.

2-methyl-4,6-bis(3-nitrophenyl)pyridine (3o):

Yield 46% (38.5 mg); white solid; mp 205–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.94 (s, 1H), 8.55 (s, 1H), 8.44 (d, J = 7.6 Hz, 1H), 8.37–8.28 (m, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.78–7.66 (m, 2H), 7.45 (s, 1H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.1, 155.3, 148.9, 148.8, 147.6, 140.9, 140.1, 133.0, 132.9, 130.3, 129.8, 123.8(4), 123.7(8), 122.1(0), 122.0(5), 120.9, 115.9, 24.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{13}N_3NaO_4$: 358.0798; found: 358.0796.

2-methyl-4,6-di(naphthalen-2-yl)pyridine (3p):

Yield 47% (40.5 mg); white solid; mp 239–241 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.55 (s, 1H), 8.22 (dd, J = 8.4, 1.6 Hz, 1H), 8.17 (s, 1H), 7.99–7.92 (m, 5H), 7.91–7.83 (m, 2H), 7.81 (dd, J = 8.8, 1.6 Hz, 1H), 7.58–7.48 (m, 4H), 7.45 (s, 1H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.0, 157.5, 149.4, 137.1, 136.1, 133.6, 133.5(2), 133.4(7), 133.4, 128.8, 128.7, 128.4(x 2), 127.7(1), 127.6(5), 126.7, 126.6, 126.4(4), 126.3(8), 126.3(7), 126.2, 124.9, 124.8, 120.0, 116.5, 24.9; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{26}H_{19}NNa$: 368.1410; found: 368.1409.

2-methyl-4,6-di(thiophen-2-yl)pyridine (3q):

Yield 82% (52.7 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68–7.60 (m, 2H), 7.52 (dd, J = 4.0, 1.2 Hz, 1H), 7.44–7.36 (m, 2H), 7.21 (s, 1H), 7.17–7.08 (m, 2H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.0, 152.6, 144.8, 142.3, 141.5, 128.3, 127.9, 127.4, 126.9, 125.2, 124.6, 117.9, 112.5, 24.5; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{12}NS_2$: 258.0406; found: 258.0408.

2-methyl-4,6-di(thiophen-3-yl)pyridine (3r):

Yield 66% (42.4 mg); yellow solid; mp 68–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, J = 2.0 Hz, 1H), 7.71–7.65 (m, 2H), 7.60 (s, 1H), 7.49–7.43 (m, 2H), 7.40 (dd, J = 4.8, 2.8 Hz, 1H), 7.25 (s, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.9, 153.6, 143.8, 142.3, 140.0, 126.9, 126.4, 126.2, 125.9, 123.7, 122.8, 118.7, 115.0,

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24.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{12}NS_2$: 258.0406; found: 258.0407.

7-methyl-5,6,8,9-tetrahydrodibenzo[*c,h*]acridine (3s):

Yield 91% (67.6 mg); brown solid; mp 185–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.57 (dd, J = 7.6, 0.8 Hz, 2H), 7.45–7.39 (m, 2H), 7.36–7.30 (m, 2H), 7.26 (d, J = 7.2 Hz, 2H), 2.99 (s, 8H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.3, 137.5, 135.4, 129.5, 129.5, 128.4, 127.3, 126.9, 125.3, 28.0, 24.6, 14.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{20}N$: 298.1590; found: 298.1595.

2-phenyl-4,6-di-p-tolylpyridine (3t):

Yield 79% (66.2 mg); yellow solid; mp 69–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.54–7.44 (m, 2H), 7.40 (d, J = 7.2 Hz, 3H), 7.34–7.27 (m, 5H), 7.22–7.18 (m, 1H), 3.54 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.4, 150.0, 139.6, 139.2, 138.9, 136.9, 129.4, 129.0, 128.8, 128.7, 128.2, 127.2, 127.0, 126.8, 116.5, 57.9, 21.3; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{21}NNa$: 358.1566; found: 358.1573.

Conflicts of interest

There are no conflicts to declare.

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