RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2017, **7**, 13123

Acid-catalyzed tandem reaction for the synthesis of pyridine derivatives *via* C=C/C(sp^3)–N bond cleavage of enones and primary amines†

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Received 18th January 2017
Accepted 17th February 2017

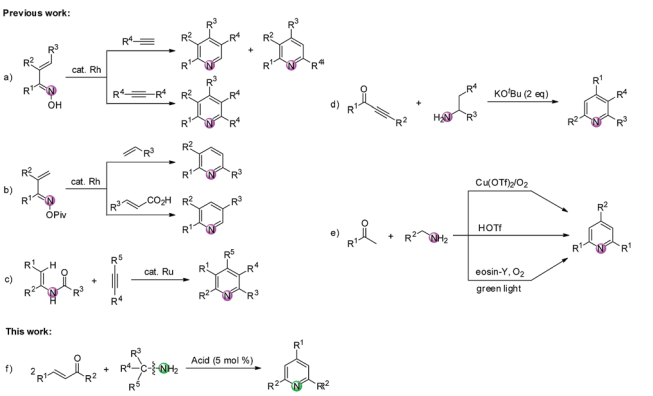
DOI: 10.1039/c7ra00780a

rsc.li/rsc-advances

A one-pot acid-catalyzed tandem reaction has been developed without any metallic reagents or extra oxidants. This reaction involves a C=C bond cleavage of enones *via* a "masked" reverse Aldol reaction, and C(sp^3)–N bond cleavage of primary amines to provide nitrogen sources for the assembly of pyridine derivatives in high yields with excellent functional group tolerance.

Introduction

Construction of *N*-heterocycles is one of the most significant areas in synthetic organic chemistry. Among them, the development of efficient methods for building the pyridine motif has attracted considerable attention since pyridine forms the structural core of numerous natural products,[1] pharmaceuticals,[2] and functionalized materials.[3] During the past decades, abundant methodologies have been disclosed for the construction of pyridine rings, in which a variety of nitrogen-containing substrates were used as building blocks.[4,5] As we know, the nitrogen source of pyridine rings can be provided by compounds containing C≡N, C=N and C–N bonds.[6] Among them, the metal-mediated [2 + 2 + 2] cycloaddition reaction constitutes a powerful tool for the synthesis of pyridines from nitriles and alkynes.[7] In addition, the transition-metal-catalyzed intermolecular reactions of compounds bearing a C=N group (imines, oximes, oxime esters, *etc.*) and carbon–carbon unsaturated compounds (*e.g.*, alkynes, alkenes, acrylic acids) have been extensively studied and have become a fascinating method to construct pyridines.[8–10] For example, Cheng[8] and Ellman[9] groups respectively reported the Rh-catalyzed C–H functionalization of α,β-unsaturated ketoximes with alkynes to produce substituted pyridines (Scheme 1a). Another Rh-catalyzed C–H functionalization of unsaturated oxime esters with alkenes or acrylic acids was reported by Rovis' group (Scheme 1b).[10] Moreover, compounds tethered with C(sp^2)–N and C(sp^3)–N bonds have also been widely utilized as nitrogen-containing substrates for building pyridines.[11–13] For instance, Wang and colleagues accomplished an impressive work that highly substituted pyridines were efficiently constructed *via* a Ru-catalyzed dehydrative [4 + 2] cycloaddition of enamides and alkynes (Scheme 1c).[11] Cui's group disclosed a base-promoted synthesis of polysubstituted pyridines from 1-arylethylamines and ynones through the β-C(sp^3)–H functionalization of enaminones (Scheme 1d).[12] Recently, Jiang, Yi and Dhavale groups respectively reported the synthesis of 2,4,6-trisubstituted pyridines from ketones and amines (Scheme 1e).[13] Nevertheless, it is rarely reported to construct pyridine rings *via* C(sp^3)–N bond cleavage of diverse primary amines providing the nitrogen source. Therefore, we herein present a route through tandem reverse Aldol reaction/condensation/cyclization/aromatization for the formation of pyridine derivatives *via* C=C/C(sp^3)–N bond cleavage of enones/primary amines. This new reaction system avoids the use of costly catalyst and extra oxidant with broad functional group tolerance at the cost of a catalytic amount of Brønsted acid in the absence of any transitional metal (Scheme 1f).



Scheme 1 Comparison of previous study and our work.

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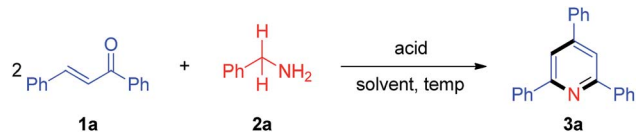
† Electronic supplementary information (ESI) available: Experimental procedure, spectral data for all products, and X-ray crystallographic files (CIF) for **3a** and **3k**. CCDC 1498096 and 1498097. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra00780a

Results and discussion

We initiated our research on the model reaction of enone **1a** with primary amine **2a** for screening optimum reaction conditions (Table 1). The desired product **3a** was obtained in 51% isolated yield upon treatment of a 1 : 1 mixture of **1a** and **2a** with 5 mol% TfOH in xylene at 100 °C for 2 h (Table 1, entry 1). We subsequently varied the reaction temperature from 100 to 130 °C, which showed that 130 °C is optimal for this protocol (Table 1, entries 2–4). Compared with 5 mol% TfOH, the yield of **3a** was not distinctly improved as the amount of TfOH was increased to 10 mol% (Table 1, entry 5). When TfOH was replaced by other acids (*e.g.*, $PhCO_2H$, AcOH, PivOH, HCl, TFA, TsOH, MsOH), the yield of **3a** remarkably decreased (Table 1, entries 6–12). Without any acids, TLC analysis indicated no desired product formation (Table 1, entry 13). Furthermore, several different solvents were also surveyed (*e.g.*, DMF, DMSO, NMP, MeCN and 1,4-dioxane), and the results revealed that xylene is the optimal solvent for this reaction (Table 1, entry 4 *vs.* entries 14–18).

With the optimal reaction conditions in hand, we proceeded to explore the nitrogen source scope for this reaction, as shown in Table 2. The aromatic methylamines (**2b–2f**) as nitrogen sources gave the desired pyridine **3a** in high yields. Moreover, treatment of **1a** with various aliphatic amines (**2g–2k**) produced **3a** in 40–71% yields, but *tert*-butylamine (**2l**) could not provide the nitrogen atom for the synthesis of pyridine **3a**. These results indicate that at least one hydrogen atom at α-position of amino is necessary for this reaction.

Table 1 Optimization of the reaction conditions[a]

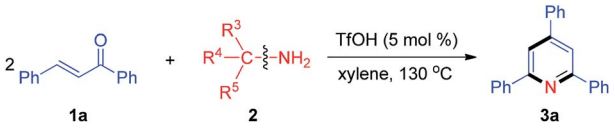


1a 2a 3a

Entry	Acid	Solvent	Temp. (°C)	Yield[b] (%)
1	TfOH	Xylene	100	51
2	TfOH	Xylene	110	72
3	TfOH	Xylene	120	85
4	**TfOH**	**Xylene**	**130**	**92**
5[c]	TfOH	Xylene	130	93
6	$PhCO_2H$	Xylene	130	33
7	AcOH	Xylene	130	37
8	PivOH	Xylene	130	28
9	HCl	Xylene	130	68
10	TFA	Xylene	130	87
11	TsOH	Xylene	130	76
12	MsOH	Xylene	130	81
13	—	Xylene	130	n.d.[d]
14	TfOH	DMF	130	46
15	TfOH	DMSO	130	33
16	TfOH	NMP	130	39
17	TfOH	CH_3CN	130	70
18	TfOH	1,4-Dioxane	130	82

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), acid (5 mol%) and solvent (1 mL) for 2 h. [b] Isolated yield. [c] 10 mol% TfOH. [d] Not detected.

Table 2 Scope of [N] sources for the reaction[a]



1a 2 3a

[N] source	R^3	R^4	R^5	Yield of **3a**[b] (%)
2b	4-$MeOC_6H_4$	H	H	95
2c	4-$F_3CC_6H_4$	H	H	88
2d	2-Furyl	H	H	81
2e	2-Thienyl	H	H	86
2f	Bn	H	H	77
2g	Et	H	H	56
2h	Me	Me	H	40
2i	i-Pr	H	H	63
2j	i-Bu	H	H	67
2k	3-Heptyl	H	H	71
2l	Me	Me	Me	n.r.[c]

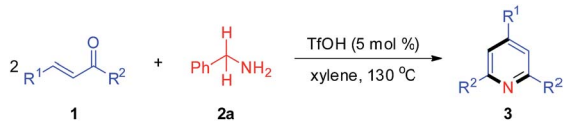
[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), TfOH (5 mol%) and xylene (1 mL) for 2 h. [b] Isolated yield. [c] No reaction.

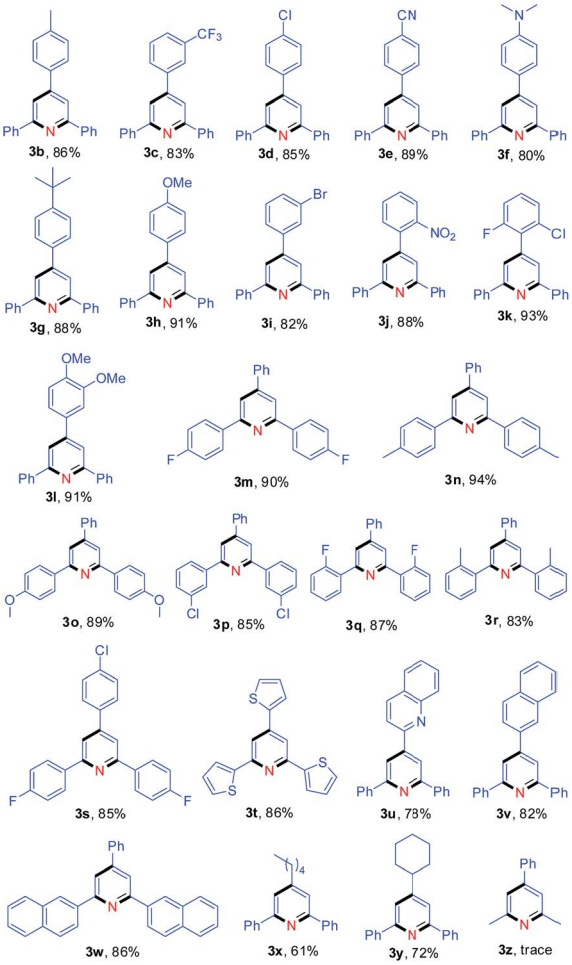
Subsequently, the scope of enones was investigated under the optimal conditions (Table 3). Enones containing one or more electron-withdrawing groups (EWG = F, Cl, Br, CF_3, CN, NO_2) or electron-donating groups (EDG = Me, ^{t}Bu, $N(Me)_2$, OMe) on the phenyl ring (R^1) are both well-tolerated and afforded excellent yields (80–93%, **3b–3l**). Variation of the electronic properties of the substituents on the aromatic ring (R^2) has little influence on the reaction efficiency (**3m–3r**). Notably, 4,4′-dihalogen substituted aryl enone also proceeded smoothly with 85% yield (**3s**). Gratifyingly, enones bearing heterocycle and fused ring reacted efficiently as well to give the corresponding product **3t–3w** in 78–86% yields. With respect to aromatic rings, the alkyl-substituted enones were also tolerated in this transformation, generating the corresponding 2,4,6-trisubstituted pyridines **3x** and **3y** in 61% and 72% isolated yields, respectively. Unfortunately, benzalacetone failed to afford the desired product **3z**. The structures of **3a** and **3k** were unambiguously confirmed by single-crystal X-ray diffraction analysis (Fig. 1).[14]

With the aim of evaluating the practicality of this catalytic process, a gram-scale experiment was performed with **1a** (10 mmol) and **2a** (15 mmol was added in two portions), yielding the corresponding product **3a** in 72% (Scheme 2).

To gain insight into the mechanism of this new reaction, we conducted several control experiments (Scheme 3). When the model substrates **1a**, and **2a** were reacted under argon atmosphere in xylene at 130 °C, we failed to obtain the product **3a**. The reaction of **1a** with **2a** under oxygen atmosphere resulted in the formation of **3a** with 91% isolated yield. The results replacing air with Ar or O_2 demonstrated that molecular oxygen is essential as an oxidant for this transformation. Under the standard conditions, the reaction of **4** with **1a** and **2a** afforded **3a** in 89% isolated yield, and the reaction of **5** with **1a** and **2a** afforded **6**, **3a** and **3n**, indicating that acetophenone should be a reactive intermediate in this process.

Table 3 Scope of enones[a]





[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), TfOH (5 mol%) and xylene (1 mL) for 2 h. Isolated yields are shown.

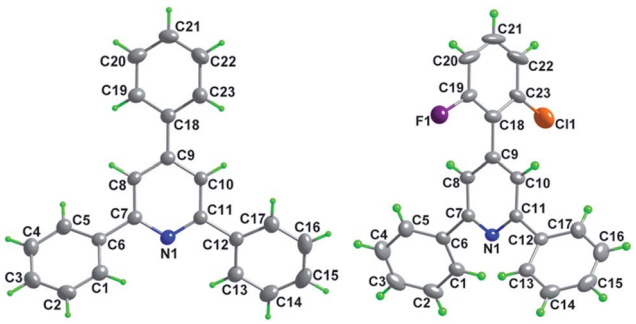
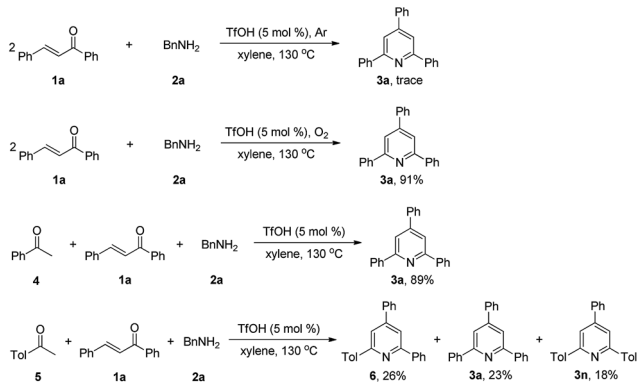


Fig. 1 X-ray crystal structures of **3a** (CCDC 1498096) and **3k** (CCDC 1498097).

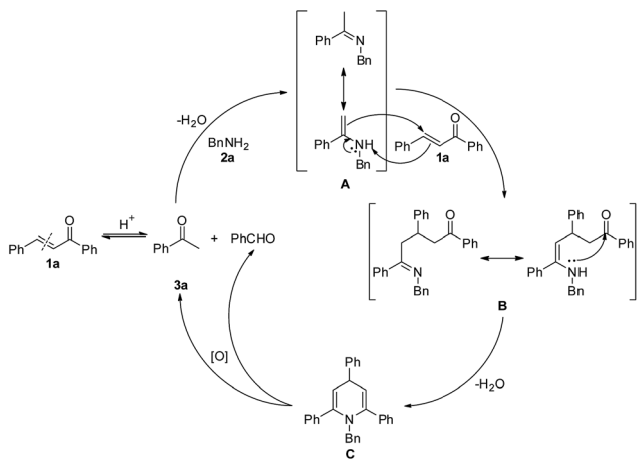
Scheme 2 Gram scale synthesis.



Scheme 3 Control experiments.

The above results have led us to propose a reaction mechanism, which is depicted in Scheme 4 using **3a** as a representative example. Originally with Brønsted acid catalysis, the reverse Aldol reaction of **1a** proceeds to give acetophenone, which reacts with **2a** to obtain the dehydrative condensation product imine **A**. Then, 1,4-addition of imine **A** to another molecule of **1a** generates intermediate **B**. Subsequent intramolecular nucleophilic addition and dehydration of intermediate **B** affords 1,4-dihydropyridine **C**. Finally, aerobic oxidative C(sp^3)–N bond cleavage of dihydropyridine **C** leads to its aromatization, with the latter being the driving force of this oxidation.

According to the mechanism proposed in Scheme 4, the reaction of (*E*)-chalcone to acetophenone and benzaldehyde is reversible, the decomposition of **C** would give the desired pyridine and benzaldehyde. If substituted $BnNH_2$ (such as *p*-tolylmethanamine) was used, "unsymmetric" chalcone would



Scheme 4 Possible mechanism.

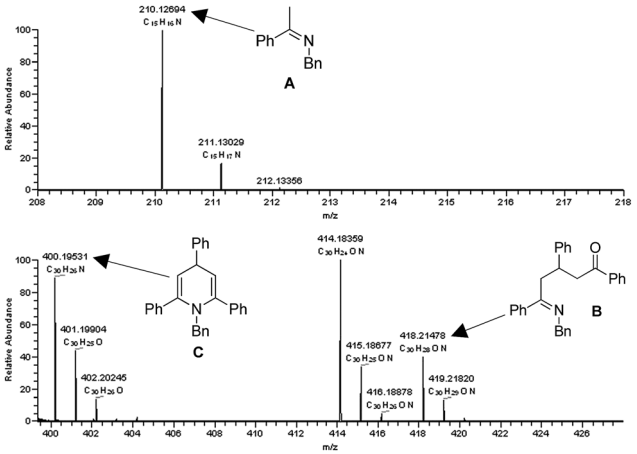


Fig. 2 ESI-MS based analysis during the formation of **3a**.

generated. As a result, the generated "unsymmetric" chalcone would react with acetophenone and benzyl amine to form pyridines with 4-different substituent. In fact, we did not obtain the 4-different substituent pyridines, because it is adverse that ketones with aldehydes perform an Aldol reaction at this reaction temperature (130 °C).

ESI/MS experiments were performed to gain evidence for the possible intermediates in the proposed mechanism. A mixture of **1a** (0.5 mmol), **2a** (0.5 mmol) and TfOH (5 mol%) in xylene (1 mL) was reacted at 130 °C for 15 min and 50 μL of the mixture was used for the ESI analysis in MeOH. The ESI/MS analyses showed three peaks at *m*/*z* 210.1269, *m*/*z* 418.2148, and *m*/*z* 400.1953 which were respectively identified as imine **A**, intermediate **B**, and dihydropyridine **C** (Fig. 2).

Conclusions

In summary, we have demonstrated an expedient approach for the synthesis of 2,4,6-trisubstituted pyridines *via* sequential reverse Aldol reaction/dehydrative condensation/addition–cyclization/aromatization, catalyzed by Brønsted acid. The use of naturally abundant air as an oxidant, readily available starting materials including the nitrogen source, and experimentally convenient catalytic process are the additional advantages of the present protocol. Further investigations on the synthetic applications of this reaction are ongoing in our laboratory.

Experimental

General experimental details

Unless otherwise noted, commercial reagents were used without further purification. All manipulations were performed under an air atmosphere unless otherwise statement. Reaction temperatures were controlled using IKAmag temperature modulator. Column chromatography was performed on silica gel (300–400 mesh). NMR spectra were obtained using a Bruker 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.00) or tetramethylsilane (TMS δ 0.00) was used as a reference. High resolution mass spectra (HRMS) were recorded on the Exactive Mass Spectrometer equipped with ESI ionization source.

General experimental procedure for the synthesis of pyridines 3

The reaction mixture of enones **1** (0.5 mmol), primary amines **2** (0.5 mmol) and TfOH (5 mol%) in xylene (1 mL) was stirred at 130 °C for 2 h in test tube, and periodically monitored by TLC. Upon completion, the crude product was cooled to room temperature and then directly separated by flash column chromatography on silica gel to give the pure product **3**.

2,4,6-Triphenylpyridine (3a). White solid (71 mg, 92%), mp 137.0–137.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.1 Hz, 4H), 7.94 (s, 2H), 7.79 (d, J = 7.0 Hz, 2H), 7.62–7.48 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.1, 139.5, 138.9, 129.0, 129.0, 128.9, 128.6, 127.1, 127.1, 117.0; HRMS (ESI) for $C_{23}H_{18}N$ ($[M + H]^+$): calcd 308.1434, found 308.1432.

2,6-Diphenyl-4-(*p*-tolyl)pyridine (3b). White solid (69 mg, 86%), mp 118.5–120.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.1 Hz, 4H), 7.93 (s, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.62–7.56 (m, 4H), 7.54–7.49 (m, 2H), 7.38 (d, J = 7.9 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 149.9, 139.6, 139.0, 135.9, 129.7, 128.9, 128.6, 127.1, 126.9, 116.8, 21.2; HRMS (ESI) for $C_{24}H_{20}N$ ($[M + H]^+$): calcd 322.1590, found 322.1590.

2,6-Diphenyl-4-(3-(trifluoromethyl)phenyl)pyridine (3c). Pale yellow solid (78 mg, 83%), mp 125.8–127.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.1 Hz, 4H), 7.99 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.88 (s, 2H), 7.75 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.56–7.45 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 148.8, 140.0, 139.2, 131.6 (q, $^2J_{C-F}$ = 32.6 Hz) 130.53, 129.7, 129.3, 128.8, 127.2, 125.6 (q, $^3J_{C-F}$ = 3.7 Hz), 124.0 (q, $^1J_{C-F}$ = 270.8 Hz), 124.0 (q, $^3J_{C-F}$ = 3.8 Hz), 117.0; HRMS (ESI) for $C_{24}H_{17}NF_3$ ($[M + H]^+$): calcd 376.1308, found 376.1306.

4-(4-Chlorophenyl)-2,6-diphenylpyridine (3d). White solid (73 mg, 85%), mp 124.3–125.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 7.0 Hz, 4H), 7.84 (s, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.56–7.47 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 148.9, 139.3, 137.4, 135.1, 129.3, 129.1, 128.7, 128.4, 127.1, 116.7; HRMS (ESI) for $C_{23}H_{17}NCl$ ($[M + H]^+$): calcd 342.1044, found 342.1042.

4-(2,6-Diphenylpyridin-4-yl)benzonitrile (3e). White solid (74 mg, 89%), mp 190.8–192.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.0 Hz, 4H), 7.78 (d, J = 8.8 Hz, 6H), 7.57–7.45 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 147.9, 143.2, 138.9, 132.7, 129.3, 128.7, 127.7, 127.0, 118.4, 116.6, 112.5; HRMS (ESI) for $C_{24}H_{17}N_2$ ($[M + H]^+$): calcd 333.1386, found 333.1385.

4-(2,6-Diphenylpyridin-4-yl)-*N*,*N*-dimethylaniline (3f). Pale yellow solid (70 mg, 80%), mp 120.1–121.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.1 Hz, 4H), 7.91 (s, 2H), 7.72 (d, J = 8.9 Hz, 2H), 7.56 (t, J = 7.4 Hz, 4H), 7.51–7.45 (m, 2H), 6.86 (d, J = 8.9 Hz, 2H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 151.0, 149.8, 140.0, 128.7, 128.6, 127.7, 127.1, 125.9, 115.9, 112.4, 40.2; HRMS (ESI) for $C_{25}H_{23}N_2$ ($[M + H]^+$): calcd 351.1856, found 351.1844.

4-(4-(*tert*-Butyl)phenyl)-2,6-diphenylpyridine (3g). White solid (80 mg, 88%), mp 87.2–88.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 7.5 Hz, 4H), 8.02 (s, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.67 (t, J = 8.0 Hz, 6H), 7.58 (t, J = 7.2 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 152.0, 149.8, 139.5, 135.9, 128.8, 128.5, 127.0, 126.7, 125.9, 116.8, 34.5, 31.2; HRMS (ESI) for $C_{27}H_{26}N$ ($[M + H]^+$): calcd 364.2060, found 364.2045.

4-(4-Methoxyphenyl)-2,6-diphenylpyridine (3h). White solid (77 mg, 91%), mp 102.5–104.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.2 Hz, 4H), 7.89 (s, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.58 (t, J = 7.4 Hz, 4H), 7.51 (t, J = 7.3 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 157.2, 149.4, 139.6, 131.0, 128.9, 128.6, 128.2, 127.0, 116.4, 114.4, 55.2; HRMS (ESI) for $C_{24}H_{20}ON$ ($[M + H]^+$): calcd 338.1539, found 338.1537.

4-(3-Bromophenyl)-2,6-diphenylpyridine (3i). White solid (79 mg, 82%), mp 106.3–107.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.0 Hz, 4H), 7.89 (t, J = 1.8 Hz, 1H), 7.84 (s, 2H), 7.66 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 7.61 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.56–7.52 (m, 4H), 7.49–7.45 (m, 2H), 7.40 (t, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 148.6, 141.2, 139.3, 131.9, 130.6, 130.2, 129.2, 128.7, 127.1, 125.8, 123.2, 116.9; HRMS (ESI) for $C_{23}H_{17}NBr$ ($[M + H]^+$): calcd 386.0539, found 386.0538.

4-(2-Nitrophenyl)-2,6-diphenylpyridine (3j). White solid (78 mg, 88%), mp 111.5–112.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.15 (m, 4H), 8.02 (dd, J = 8.1, 1.1 Hz, 1H), 7.72–7.68 (m, 1H), 7.63 (s, 2H), 7.62–7.57 (m, 1H), 7.54–7.49 (m, 5H), 7.48–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 148.7, 147.3, 139.0, 134.6, 132.9, 131.5, 129.4, 129.2, 128.7, 127.1, 124.5, 117.8; HRMS (ESI) for $C_{23}H_{17}O_2N_2$ ($[M + H]^+$): calcd 353.1284, found 353.1284.

4-(2-Chloro-6-fluorophenyl)-2,6-diphenylpyridine (3k). White solid (84 mg, 93%), mp 177.8–178.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26–8.23 (m, 4H), 7.76 (s, 2H), 7.59–7.52 (m, 4H), 7.51–7.45 (m, 2H), 7.41–7.32 (m, 2H), 7.17 (ddd, J = 9.3, 7.6, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (d, $^1J_{C-F}$ = 250.1 Hz), 157.0, 142.1, 139.2, 133.9 (d, $^3J_{C-F}$ = 4.0 Hz), 130.1 (d, $^2J_{C-F}$ = 9.4 Hz), 129.1, 128.7, 127.1, 126.9, 125.7 (d, $^3J_{C-F}$ = 3.5 Hz), 120.1 (d, $^4J_{C-F}$ = 1.0 Hz), 114.5 (d, $^2J_{C-F}$ = 22.7 Hz); HRMS (ESI) for $C_{23}H_{16}NClF$ ($[M + H]^+$): calcd 360.0950, found 360.0950.

4-(3,4-Dimethoxyphenyl)-2,6-diphenylpyridine (3l). White solid (84 mg, 91%), mp 99.8–101.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.4 Hz, 4H), 7.79 (s, 2H), 7.48 (t, J = 7.5 Hz, 4H), 7.41 (t, J = 7.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 1H), 7.19 (t, J = 3.0 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 149.8, 149.8, 149.3, 139.5, 131.6, 128.9, 128.5, 127.0, 119.7, 116.6, 111.4, 110.1, 56.0, 55.9; HRMS (ESI) for $C_{25}H_{22}O_2N$ ($[M + H]^+$): calcd 368.1645, found 368.1645.

2,6-Bis(4-fluorophenyl)-4-phenylpyridine (3m). White solid (77 mg, 90%), mp 178.1–178.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.14 (m, 4H), 7.80 (s, 2H), 7.72 (d, J = 6.7 Hz, 2H), 7.58–7.48 (m, 3H), 7.25–7.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{C-F}$ = 248.6 Hz), 156.3, 150.3, 138.7, 135.5 (d, $^4J_{C-F}$ = 3.1 Hz), 129.1, 129.0, 128.8 (d, $^3J_{C-F}$ = 8.3 Hz), 127.1, 116.5, 115.5 (d, $^2J_{C-F}$ = 21.5 Hz); HRMS (ESI) for $C_{23}H_{16}NF_2$ ($[M + H]^+$): calcd 344.1245, found 344.1245.

4-Phenyl-2,6-di-*p*-tolylpyridine (3n). White solid (79 mg, 94%), mp 162.8–163.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.1 Hz, 4H), 7.87 (s, 2H), 7.77 (d, J = 7.0 Hz, 2H), 7.58–7.47 (m, 3H), 7.36 (d, J = 8.0 Hz, 4H), 2.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 150.0, 139.2, 138.9, 136.8, 129.4, 129.0, 128.8, 127.1, 127.0, 116.5, 21.27; HRMS (ESI) for $C_{25}H_{22}N$ ($[M + H]^+$): calcd 336.1747, found 336.1739.

2,6-Bis(4-methoxyphenyl)-4-phenylpyridine (3o). White solid (82 mg, 89%), mp 129.5–131.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 4H), 7.72 (s, 2H), 7.68 (d, J = 7.0 Hz, 2H), 7.50–7.39 (m, 3H), 7.01 (d, J = 8.8 Hz, 4H), 3.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 156.7, 149.7, 139.1, 132.2, 128.9, 128.6, 128.2, 127.0, 115.4, 113.9, 55.1; HRMS (ESI) for $C_{25}H_{22}O_2N$ ($[M + H]^+$): calcd 368.1645, found 368.1644.

2,6-Bis(3-chlorophenyl)-4-phenylpyridine (3p). White solid (80 mg, 85%), mp 180.5–181.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.14 (m, 2H), 8.04 (ddd, J = 6.2, 2.9, 1.7 Hz, 2H), 7.83 (s, 2H), 7.74–7.69 (m, 2H), 7.57–7.41 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 150.4, 141.0, 138.3, 134.8, 129.9, 129.2, 129.1 (2), 127.1 (2), 125.1, 117.5; HRMS (ESI) for $C_{23}H_{16}NCl_2$ ($[M + H]^+$): calcd 376.0654, found 376.0644.

2,6-Bis(2-fluorophenyl)-4-phenylpyridine (3q). White solid (75 mg, 87%), mp 117.3–118.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (t, J = 7.3 Hz, 2H), 7.96 (s, 2H), 7.68 (d, J = 7.3 Hz, 2H), 7.47–7.29 (m, 5H), 7.24 (t, J = 7.4 Hz, 2H), 7.13 (dd, J = 10.9, 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (d, $^1J_{C-F}$ = 249.8 Hz), 153.5 (d, $^4J_{C-F}$ = 2.3 Hz), 149.3, 138.4, 131.3 (d, $^4J_{C-F}$ = 2.8 Hz), 130.4 (d, $^3J_{C-F}$ = 8.6 Hz), 129.0, 128.9, 127.4 (d, $^2J_{C-F}$ = 11.3 Hz), 127.2, 124.4 (d, $^3J_{C-F}$ = 3.5 Hz), 121.3 (d, $^3J_{C-F}$ = 9.7 Hz), 116.1 (d, $^2J_{C-F}$ = 23.1 Hz); HRMS (ESI) for $C_{23}H_{16}NF_2$ ($[M + H]^+$): calcd 344.1245, found 344.1234.

4-Phenyl-2,6-di-*o*-tolylpyridine (3r). White solid (70 mg, 83%), mp 132.2–133.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.0 Hz, 2H), 7.65 (s, 2H), 7.59–7.47 (m, 5H), 7.38–7.32 (m, 6H), 2.55 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 148.7, 140.7, 138.4, 135.8, 130.6, 129.8, 129.1, 129.0, 128.2, 127.1, 125.8, 120.0, 20.58; HRMS (ESI) for $C_{25}H_{22}N$ ($[M + H]^+$): calcd 336.1747, found 336.1733.

4-(4-Chlorophenyl)-2,6-bis(4-fluorophenyl)pyridine (3s). White solid (80 mg, 85%), mp 207.0–208.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.13 (m, 4H), 7.76 (s, 2H), 7.68–7.62 (m, 2H), 7.53–7.47 (m, 2H), 7.23–7.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, $^1J_{C-F}$ = 248.9 Hz), 156.6, 149.2, 137.2, 135.4 (d, $^4J_{C-F}$ = 2.8 Hz), 129.4, 128.9 (d, $^3J_{C-F}$ = 8.3 Hz), 128.4, 127.1, 116.3, 115.6 (d, $^2J_{C-F}$ = 21.6 Hz); HRMS (ESI) for $C_{23}H_{15}NClF_2$ ($[M + H]^+$): calcd 378.0856, found 378.0855.

2,4,6-Tri(thiophen-2-yl)pyridine (3t). White solid (70 mg, 86%), mp 129.9–131.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 3.7, 1.1 Hz, 2H), 7.65 (s, 2H), 7.56 (dd, J = 3.7, 1.1 Hz, 1H), 7.43 (ddd, J = 4.0, 2.9, 1.1 Hz, 3H), 7.17–7.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 144.6, 142.8, 141.2, 128.3, 127.9, 127.8, 127.0, 125.4, 124.9, 113.1; HRMS (ESI) for $C_{17}H_{12}NS_3$ ($[M + H]^+$): calcd 326.0126, found 326.0125.

2-(2,6-Diphenylpyridin-4-yl)quinoline (3u). Brown solid (70 mg, 78%), mp 167.2–168.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2H), 8.35–8.24 (m, 6H), 7.99 (d, J = 8.6 Hz, 1H), 7.87 (d,

$J = 8.1$ Hz, 1H), 7.82–7.77 (m, 1H), 7.63–7.53 (m, 5H), 7.48 (t, $J =$ 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.1, 148.3, 148.2, 139.5, 137.2, 130.0 (2), 129.0, 128.6, 127.8, 127.5, 127.2, 127.1, 118.6, 116.9; HRMS (ESI) for $C_{26}H_{19}N_2$ ($[M + H]^+$): calcd 359.1543, found 359.1528.

4-(Naphthalen-2-yl)-2,6-diphenylpyridine (3v). White solid (73 mg, 82%), mp 251.8–252.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, $J = 7.1$ Hz, 4H), 7.97 (d, $J = 8.1$ Hz, 2H), 7.86 (s, 2H), 7.63–7.45 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.2, 139.4, 138.1, 133.8, 131.0, 129.1, 128.8, 128.7, 128.5, 127.1, 126.7 (2), 126.2, 125.4, 120.1, 117.1; HRMS (ESI) for $C_{27}H_{20}N$ ($[M + H]^+$): calcd 358.1590, found 358.1589.

2,6-Di(naphthalen-2-yl)-4-phenylpyridine (3w). White solid (88 mg, 86%), mp 159.7–161.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 8.45 (dd, $J = 8.6$, 1.7 Hz, 2H), 8.08–8.01 (m, 6H), 7.93 (dd, $J = 8.1$, 4.3 Hz, 2H), 7.85–7.80 (m, 2H), 7.62–7.51 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.2, 139.0, 136.9, 133.8, 133.5, 129.1, 129.0, 128.7, 128.4, 127.7, 127.2, 126.5, 126.2, 124.9, 117.4; HRMS (ESI) for $C_{31}H_{22}N$ ($[M + H]^+$): calcd 408.1747, found 408.1732.

4-Pentyl-2,6-diphenylpyridine (3x). Pale yellow oil (46 mg, 61%), mp 190.8–192.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J = 7.1$ Hz, 4H), 7.39–7.34 (m, 6H), 7.31–7.26 (m, 2H), 2.62–2.54 (m, 2H), 1.64–1.54 (m, 2H), 1.33–1.18 (m, 4H), 0.80 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 153.1, 139.7, 128.7, 128.5, 127.0, 119.0, 35.7, 31.4, 30.2, 22.5, 13.9; HRMS (ESI) for $C_{22}H_{24}N$ ($[M + H]^+$): calcd 302.1903, found 302.1894.

4-Cyclohexyl-2,6-diphenylpyridine (3y). White solid (56 mg, 72%), mp 97.3–98.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–8.08 (m, 4H), 7.57 (s, 2H), 7.55–7.48 (m, 4H), 7.47–7.41 (m, 2H), 2.73–2.60 (m, 1H), 2.01 (d, $J = 13.0$ Hz, 2H), 1.93 (d, $J = 12.7$ Hz, 2H), 1.83 (d, $J = 12.6$ Hz, 1H), 1.63–1.42 (m, 4H), 1.40–1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 156.9, 139.9, 128.7, 128.5, 127.0, 117.6, 44.4, 33.7, 26.6, 26.0; HRMS (ESI) for $C_{23}H_{24}N$ ($[M + H]^+$): calcd 314.1903, found 314.1894.

Acknowledgements

We would like to thank the National Natural Science Foundation of China (21362002 and 81260472), Guangxi Natural Science Foundation of China (2014GXNSFDA118007 and 2016GXNSFEA380001), State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources (CMEMR2014-A02 and CMEMR2012-A20), the Fund of Guangxi Key Laboratory of Functional Phytochemicals Research and Utilization (FPRU2015-2), and Guangxi's Medicine Talented Persons Small Highland Foundation (1306).

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