HETEROCYCLES, Vol. 104, No. 8, 2022, pp. 1435 - 1446. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 26th May, 2022, Accepted, 17th June, 2022, Published online, 27th June, 2022
DOI: 10.3987/COM-22-14688

NH_4I-CATALYZED FORMAL [4+2] CYCLOADDITION OF α,β-UNSATURATED *O*-ACETYL OXIME WITH ALKYL PYRUVATE FOR RAPID SUBSTITUTED PYRIDINE FORMATION

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Abstract – A facile synthetic method to substituted pyridines has been developed via the NH_4I-catalyzed [4+2] cycloaddition of readily available oxime acetates with alkyl pyruvate. This process involves N-O bond cleavages and C-C bond formations to furnish substituted pyridines under redox-neutral conditions. The reaction features mild conditions and high functional-groups compatibility.

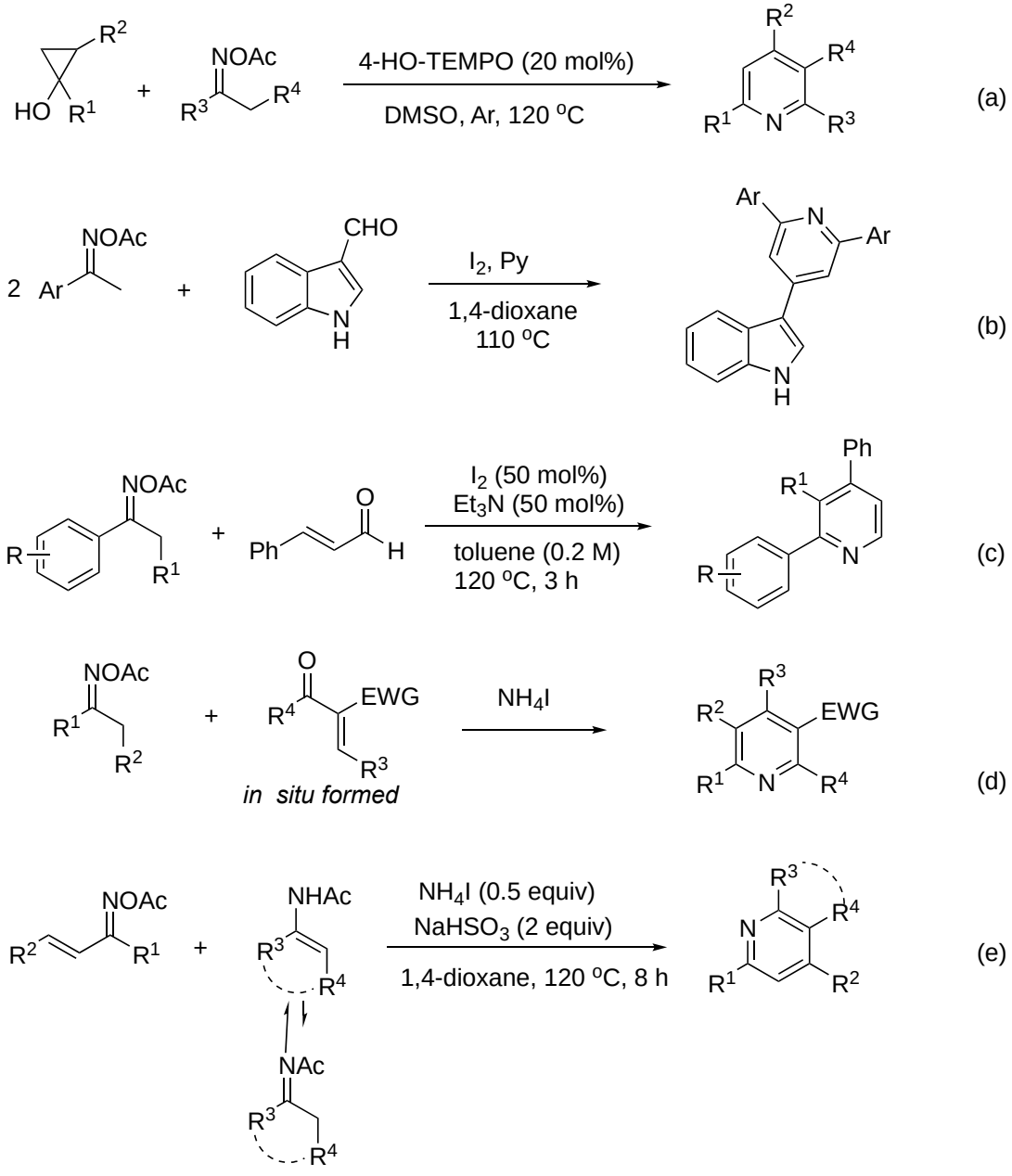
INTRODUCTION

Pyridine derivatives are significant and valuable scaffolds that occur in polymer materials,[1] coordination chemistry,[2] numerous natural products,[3] and catalysts.[4] Further, they are also used to treat some neurodegenerative diseases and applied in clinical practice.[5,6] Accordingly, great effort has been devoted to developing efficient approaches to these scaffolds by adopting several classical and modern techniques such as the condensation of carbonyl compounds with ammonia,[7] transition-metal-catalyzed C−H functionalization etc.[8]

In recent years, ketoxime acetates as an internal oxidant have proved to be versatile building blocks with a range of transition-metal catalysts, such as Pd, Cu and Co, especially for the construction of nitrogen-containing heterocycles.[9] Given sustainable development, chemical procedures under metal-free conditions are always of significance, especially in the pharmaceutical industry.[10] So far, many synthetic approaches have been developed to access nitrogen-containing heterocycles through ketoxime acetates under metal-free conditions. For example, Han reported pyridine formation through 4-HO-TEMPO-catalyzed cyclization of oxime acetates with cyclopropanols (Scheme 1a).[11] Gao and Huang have proved that I_2 was capable of triggering N–O bond cleavage of ketoxime acetates to generate iminyl radicals which react with aldehydes for the efficient preparation of pyridines (Schemes 1b and

1c).[12] Further, Deng disclosed NH_4I-initiated effective formation of polysubstituted pyridines through [3+3] annulation of oxime acetates and α,β-unsaturated ketones (Scheme 1d).[13] In 2020, Guo and coworkers further investigated the NH_4I-triggered formal [4+2] annulation of α,β-unsaturated ketoxime acetates with acetyl imine in situ-formed through tautomerization of enamide, providing efficient access to valuable highly substituted pyridines in moderate to good yields (Scheme 1e).[14]

Despite these advances, the reaction of α,β-unsaturated ketoxime acetates with ketones has not been reported under metal-free conditions. Herein, we disclose a metal-free system for the synthesis of substituted pyridines by the intermolecular assembly of α,β-unsaturated ketoximes and alkyl pyruvate.

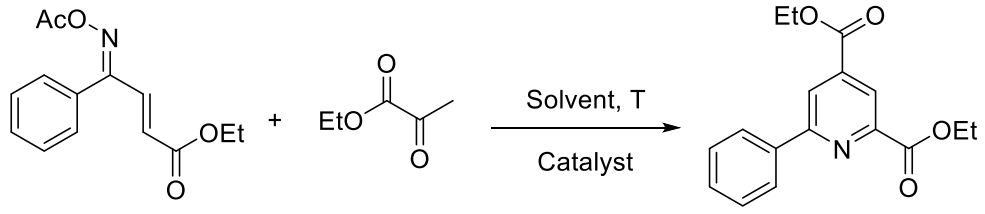


Scheme 1. Metal-free synthetic approaches for highly substituted pyridines through ketoxime acetates

RESULTS AND DISCUSSION

Initially, ketoxime-enoate (**1a**) and ethyl 2-oxopropanoate (**2a**) were chosen as the model substrates to optimize the reaction conditions. When the reaction was performed in the presence of NH_4I in toluene at 120 °C for 12 h under nitrogen atmosphere using $NaHSO_3$ as an additive, diethyl 6-phenylpyridine-2,4-dicarboxylate (**3a**) was obtained in 68% yield (Table 1, Entry 1). We next examined other iodine reagents including KI, I_2, and NIS, however, none of them gave better results than NH_4I (Table 1, Entries 2-4). Some metal catalysts, such as CuI, CuBr, CuCl, $PdCl_2$, and $FeCl_3$ were also examined, but, no better result was obtained (Table 1, Entries 5-9). Further investigation of reaction solvents revealed that toluene gave the best yield, while other solvents including THF, 1,4-dioxane, DCE and MeCN offered lower results (Table 1, Entries 10-13). Finally, the reaction temperature was investigated and after a brief screening of different temperatures, we found that the highest yield was achieved at 100 °C (Table 1, Entries 14-16).

Table 1. Optimization of the reaction conditions



1a **2a** **3a**

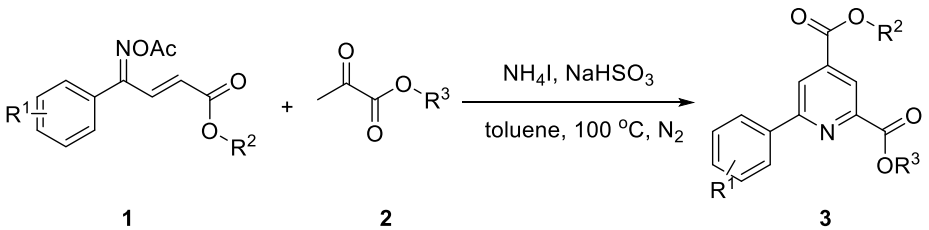
Entry	Solvent	Additive	Catalyst	Time(h)	Temp (°C)	yield (%)[a, b]
1	toluene	$NaHSO_3$	NH_4I	12	120	68
2	toluene	$NaHSO_3$	KI	12	120	0
3	toluene	$NaHSO_3$	I_2	12	120	trace
4	toluene	$NaHSO_3$	NIS	12	120	trace
5	toluene	$NaHSO_3$	CuI[c]	12	120	18
6	toluene	$NaHSO_3$	CuBr[c]	12	120	10
7	toluene	$NaHSO_3$	CuCl[c]	12	120	10
8	toluene	$NaHSO_3$	$PdCl_2$[c]	12	120	--
9	toluene	$NaHSO_3$	$FeCl_3$[c]	12	120	32
10	THF	$NaHSO_3$	NH_4I	12	120	56
11	1,4-dioxane	$NaHSO_3$	NH_4I	12	120	51
12	DCE	$NaHSO_3$	NH_4I	12	120	56
13	MeCN	$NaHSO_3$	NH_4I	12	120	40

14	toluene	$NaHSO_3$	NH_4I	12	90	54
15	toluene	$NaHSO_3$	NH_4I	12	100	72
16	toluene	$NaHSO_3$	NH_4I	12	110	70

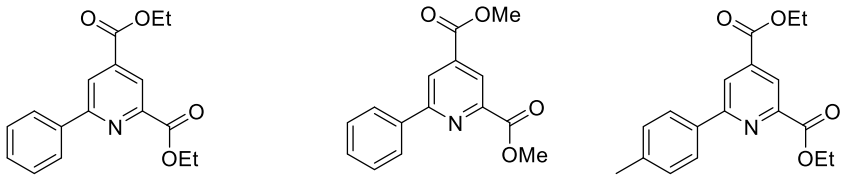
a Reagents: **1a** (1 mmol), **2a** (2 mmol), Additive (1 mmol), Catalyst (0.5 mmol), Solvent (2 mL);
b Isolated yields;
c. 0.1 mmol catalyst was used.

After establishing the optimal reaction conditions, the substrate scope and limitations of various α,β-unsaturated oxime acetates were then investigated, and the results are summarized in Table 2. Generally, a set of α,β-unsaturated oxime acetates decorated with electron-donating (Me, MeO) or electron-withdrawing (F, Cl) substituents at the *para*-, *meta*-, or *ortho*-positions on the aromatic ring were broadly tolerated and the corresponding products **3a-3h** were attained in moderate to good yields. The desired products of **3c** and **3d** were obtained in 62% and 56% yield. The α,β-unsaturated oxime acetates decorated electron-withdrawing (F, Cl) substituents at the *para*-positions on the aromatic ring give the product **3f** and **3g** in 78% and 74% yield. The above results indicated that a substrate with an electron-withdrawing substituent on the phenyl ring gave a higher yield than that with an electron-donating substituent (**3c**, **3d** *vs* **3f**, **3g**). In the case of *ortho*-methoxy-substituted substrate, the target pyridine (**3e**) was obtained in 47% yield. *meta*-Chloro-substituted substrate reacted smoothly and resulted in the target pyridine (**3h**) in 70% yield. Moreover, other ketoxime-enoates **1** with aromatic rings such as β-naphthyl also showed good reactivity in this transformation to deliver the desired product without any difficulties (**3i**). The structure of compound **3a** was confirmed by X-ray analysis.[15]

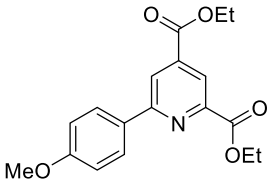
Table 2. Substrate scope of the reaction[a,b]



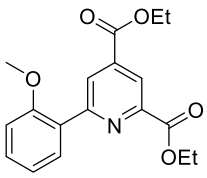
1 **2** **3**



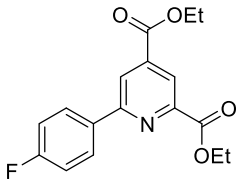
3a (72%) **3b** (65%) **3c** (62%)



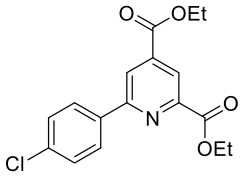
3d (56%)



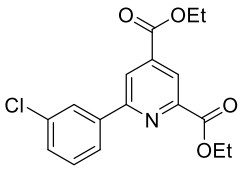
3e (47%)



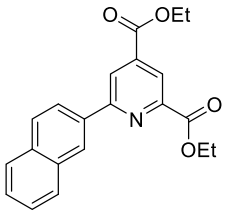
3f (78%)



3g (74%)



3h (70%)

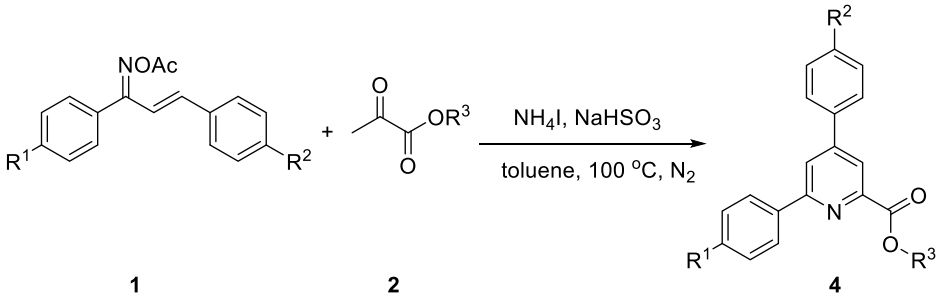


3i (64%)

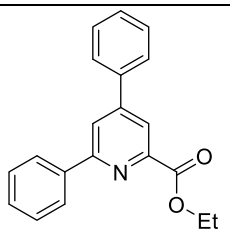
a Reagents: **1** (1 mmol), **2** (2 mmol), $NaHSO_3$ (1 mmol), NH_4I (0.5 mmol), toluene (2 mL);
b Isolated yields.

To extend the generality of this methodology, chalcone-derived oxime acetates were also subjected to the above standard conditions. Gratifyingly, chalcone-derived oxime acetates with different substituents were found to be tolerated under the standard reaction conditions. However, the reaction yields are not satisfactory. The main reason is that chalcone derived oxime acetates can react by itself under the standard reaction conditions. For example, **4A**, **4B**, **4C** and **4D** were obtained in 14%, 15%, 18% and 12% yields (Scheme 2), respectively. The structure of compound **4d** was confirmed by X-ray analysis.[16]

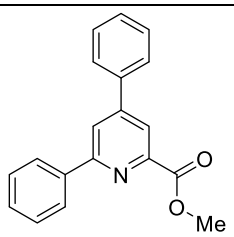
Table 3. Substrate scope of chalcone-derived oxime acetates[a,b]



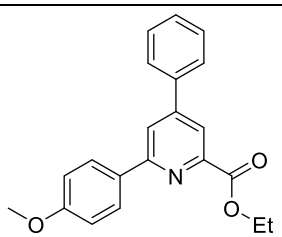
1 **2** **4**



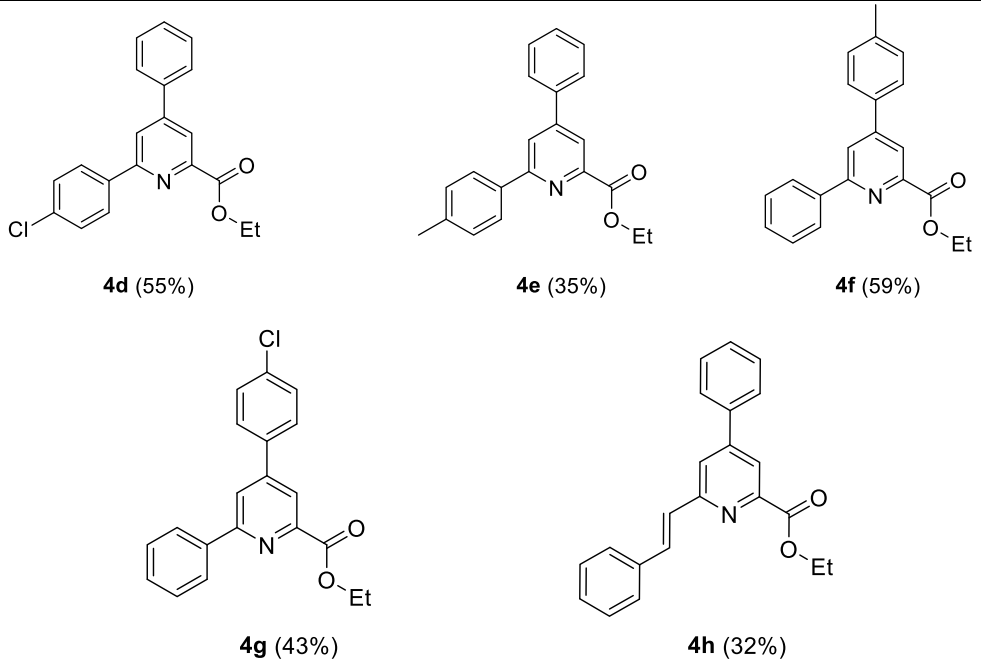
4a (46%)



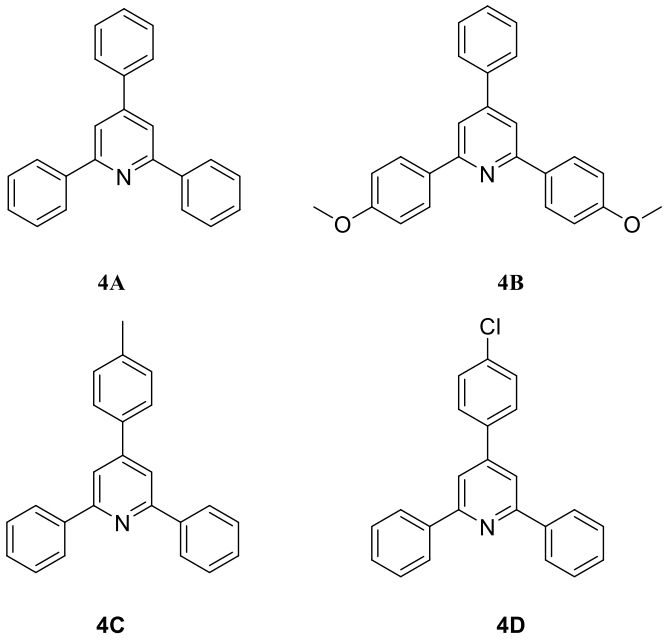
4b (42%)



4c (38%)



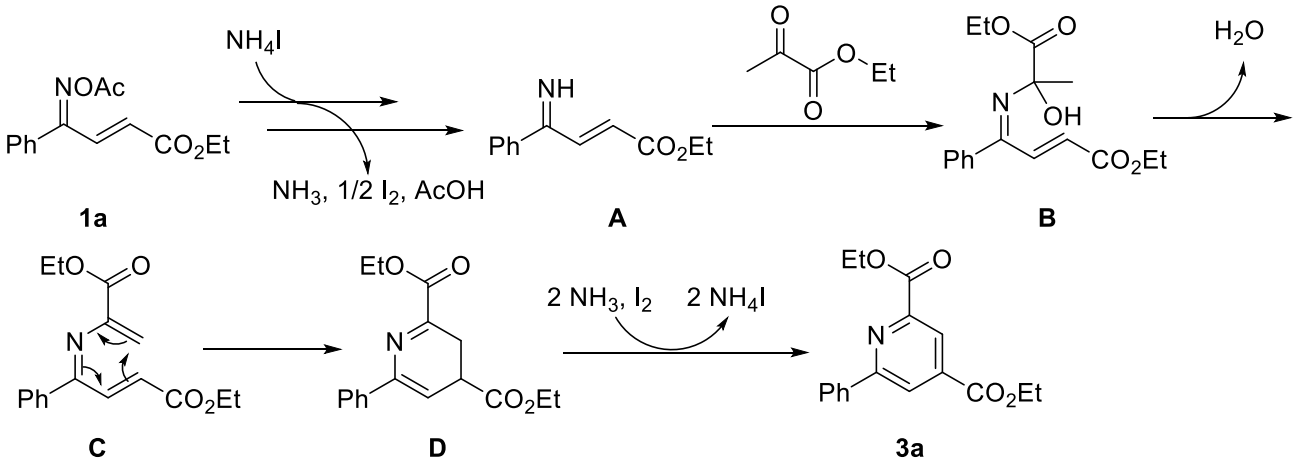
a Reagents: **1** (1 mmol), **2** (2 mmol), $NaHSO_3$ (1 mmol), NH_4I (0.5 mmol), toluene (2 mL);
b Isolated yields.



Scheme 2. Structures of **4A**, **4B**, **4C** and **4D**

On the basis of the literature,[14] a plausible mechanism was postulated for this reaction as shown in Scheme 3. Initially, NH_4I-mediated reduction of the N–O bond of ketoxime-enoate **1a** generated ketimine **A**, which subsequently underwent condensation with ethyl 2-oxopropanoate **2a** to afford the intermediate **B**. Elimination of intermediate **B** by the release of H_2O resulted in the formation of an

aza-hexa-1,3,5-triene intermediate **C**. Finally, thermal 6π-electrocyclization and rapid I_2-mediated oxidative aromatization furnished the pyridine product **3a**.



Scheme 3. Proposed mechanism

In conclusion, an efficient approach to polysubstituted pyridines in moderate to good yields from readily available α,β-unsaturated ketoxime acetates and ester pyruvate has been developed. The current transformation features mild reaction conditions and broad substrate scope.

EXPERIMENTAL

All commercial materials were used without further purification. Column chromatography was carried out on silica gel. Melting points were determined with an X-4 apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. High-resolution mass spectra (HRMS) were obtained on a waters G2-Xs with an ESI source (Waters, Manchester, UK). ^{1}H NMR spectra were recorded on 600 or 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded on 125 or 100 MHz in $CDCl_3$.

Typical procedure for the preparation of substituted pyridines

Ketoxime-enoates **1** (3.0 mmol), alkyl pyruvates **2** (6.0 mmol), NH_4I (0.22 g, 0.15 mmol) and $NaHSO_3$ (0.31 g, 3.0 mmol) were loaded into a 20 mL tube under a N_2 atmosphere. The solvent toluene (15 mL) was added into the tube by syringe. The reaction mixture was stirred at 100 ℃ for 12 h. Upon completion of the reaction, the mixture was then allowed to cool down to room temperature and flushed through a short column of silica gel with EtOAc (15 mL). After rotary evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the product.

Diethyl 6-phenylpyridine-2,4-dicarboxylate (3a) White solid; 72% yield; mp: 99-102 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.47 (s, 1H), 8.14–8.13 (m, 2H), 7.53–7.47 (m, 3H), 4.54–4.47 (m, 4H), 1.50–1.44 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 164.7, 158.7, 149.4, 139.8, 137.7, 130.0, 129.0,

127.3, 122.7, 122.4, 62.2, 62.2, 14.4, 14.3; IR (film) 2979, 2906, 1742, 1721, 1603, 1556, 1251, 1223, 1025, 757. ESI-HRMS $C_{17}H_{18}NO_4$ ([M+H]$^+$): calcd 300.1231, found 300.1241.

4-Ethyl 2-methyl 6-phenylpyridine-2,4-dicarboxylate (3b) White solid; 65% yield; mp: 107-110 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.47 (s, 1H), 8.12–8.11 (m, 2H), 7.53–7.47 (m, 3H), 4.48 (q, J = 7.2 Hz, 2H), 4.06 (s, 3H), 1.47–1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 164.6, 158.8, 149.0, 139.9, 137.7, 130.0, 129.0, 127.3, 122.9, 122.5, 62.2, 53.1, 14.3; IR (film) 3072, 2946, 1746, 1716, 1597, 1566, 1339, 1232, 754; ESI-HRMS $C_{16}H_{16}NO_4$ ([M+H]$^+$): calcd 286.1074, found 286.1077.

Diethyl 6-(*p*-tolyl)pyridine-2,4-dicarboxylate (3c) White solid; 62% yield; mp: 105-107 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.44 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.52–4.47 (m, 4H), 2.42 (s, 3H), 1.49–1.44 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 164.7, 158.7, 149.2, 140.2, 139.7, 134.9, 129.7, 127.2, 122.4, 122.1, 62.2, 62.1, 21.4, 14.4, 14.3; IR (film) 2985, 2912, 1738, 1721, 1604, 1563, 1337, 1232, 759; ESI-HRMS $C_{18}H_{20}NO_4$ ([M+H]$^+$): calcd 314.1387, found 314.1385.

Diethyl 6-(4-methoxyphenyl)pyridine-2,4-dicarboxylate (3d) White solid; 56% yield; mp: 76-77 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.40 (s, 1H), 8.12–8.10 (m, 2H), 7.03–7.02 (m, 2H), 4.53–4.46 (m, 4H), 3.88 (s, 3H), 1.49–1.44 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 164.8, 161.2, 158.3, 149.2, 139.7, 130.3, 128.7, 121.9, 121.6, 114.3, 62.1, 62.1, 55.4, 14.3, 14.3; IR (film) 2991, 1836, 1740, 1719, 1605, 1514, 1337, 1263, 759; ESI-HRMS $C_{18}H_{20}NO_5$ ([M+H]$^+$): calcd 300.1336, found 300.1339.

Diethyl 6-(2-methoxyphenyl)pyridine-2,4-dicarboxylate (3e) White solid; 47% yield; mp: 109-110 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.53 (s, 1H), 7.92–7.91 (m, 1H), 7.43–7.40 (m, 1H), 7.12–7.10 (m, 1H), 7.02–7.01 (m, 1H), 4.53–4.44 (m, 4H), 3.89 (s, 3H), 1.48–1.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 164.9, 157.5, 157.3, 149.0, 138.6, 131.6, 130.9, 127.7, 127.6, 122.1, 121.3, 111.4, 62.0, 62.0, 55.7, 14.4, 14.3; IR (film) 3097, 2974, 1721, 1608, 1437, 1254, 1237, 1027, 757; ESI-HRMS $C_{18}H_{20}NO_5$ ([M+H]$^+$): calcd 300.1336, found 300.1343.

Diethyl 6-(4-fluorophenyl)pyridine-2,4-dicarboxylate (3f) White solid; 78% yield; mp: 139-140 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53–8.53 (m, 1H), 8.42–8.41 (m, 1H), 8.15–8.13 (m, 2H), 7.21–7.18 (m, 2H), 4.54–4.47 (m, 4H), 1.49–1.45 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3 ($J_{C\text{-}F}$ = 187.8 Hz), 164.8, 164.5, 157.6, 149.4, 139.9, 133.9 ($J_{C\text{-}F}$ = 3.9 Hz), 129.3, 129.2, 122.3, 115.9 ($J_{C\text{-}F}$ = 21.5 Hz), 62.3, 62.2, 14.3, 14.3; IR (film) 2982, 2906, 1743, 1725, 1604, 1511, 1231, 1163, 763; ESI-HRMS $C_{17}H_{17}FNO_4$ ([M+H]$^+$): calcd 318.1137, found 318.1132.

Diethyl 6-(4-chlorophenyl)pyridine-2,4-dicarboxylate (3g) White solid; 74% yield; mp: 107-108 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.43 (s, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 4.54–4.47 (m, 4H), 1.50–1.45 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 164.5, 157.4, 149.4,

140.0, 136.2, 136.1, 129.2, 128.6, 122.6, 122.4, 62.3, 62.2, 14.3, 14.3; IR (film) 2982, 2904, 1746, 1723, 1603, 1560, 1369, 1336, 1243, 762; ESI-HRMS $C_{17}H_{17}ClNO_4$ ($[M+H]^+$): calcd 334.0841, found 334.0849.

Diethyl 6-(3-chlorophenyl)pyridine-2,4-dicarboxylate (3h) Light yellow solid; 70% yield; mp: 72-73 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.43 (s, 1H), 8.14 (s, 1H), 8.01–8.00 (m, 1H), 7.45–7.44 (m, 2H), 4.55–4.47 (m, 4H), 1.50–1.45 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 164.4, 157.2, 149.5, 140.1, 139.5, 135.1, 130.2, 129.9, 127.5, 125.4, 122.9, 122.7, 62.3, 62.3, 14.3, 14.3; IR (film) 2982, 2940, 1726, 1558, 1442, 1181, 1029, 760; ESI-HRMS $C_{17}H_{17}ClNO_4$ ($[M+H]^+$): calcd 334.0841, found 334.0843.

Diethyl 6-(naphthalen-2-yl)pyridine-2,4-dicarboxylate (3i) White solid; 64% yield; mp: 88-89 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.63–8.61 (m, 2H), 8.56 (s, 1H), 8.29–8.28 (m, 1H), 8.00–7.97 (m, 2H), 7.89–7.88 (m, 1H), 7.55–7.53 (m, 2H), 4.57–4.49 (m, 4H), 1.52–1.47 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 164.7, 158.6, 149.5, 139.9, 135.0, 134.1, 133.4, 129.0, 128.8, 127.7, 127.1, 127.1, 126.5, 124.5, 122.9, 122.4, 62.3, 62.2, 14.4, 14.3; IR (film) 2984, 2904, 1743, 1726, 1597, 1254, 1230, 1023, 760; ESI-HRMS $C_{21}H_{20}NO_4$ ($[M+H]^+$): calcd 350.1387, found 350.1383.

Ethyl 4,6-diphenylpicolinate (4a) White solid; 46% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.16–8.10 (m, 3H), 7.76–7.75 (m, 2H), 7.56–7.47 (m, 6H), 4.55 (q, J = 6.0 Hz, 2H), 1.51 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 150.4, 149.0, 138.7, 137.7, 129.5, 129.3, 128.9, 127.4, 127.2, 121.5, 121.5, 62.0, 14.4. Spectral properties were in accordance with the literature.[17]

Methyl 4-phenyl-6-(*p*-tolyl)picolinate (4b) White solid; 42% yield; mp: 96-98 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.32–8.32 (m, 1H), 8.11–8.10 (m, 3H), 7.76–7.75 (m, 2H), 7.55–7.46 (m, 6H), 4.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 158.5, 150.5, 148.6, 138.7, 137.6, 129.5, 129.5, 129.3, 128.9, 127.4, 127.2, 121.7, 121.6, 53.0; IR (film) 2951, 1738, 1715, 1600, 1260, 1235, 1150, 768; ESI-HRMS $C_{19}H_{16}NO_2$ ($[M+H]^+$): calcd 290.1176, found 290.1172.

Ethyl 6-(4-methoxyphenyl)-4-phenylpicolinate (4c) White solid; 38% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.10–8.09 (m, 2H), 8.02 (s, 1H), 7.73–7.72 (m, 2H), 7.53–7.47 (m, 3H), 7.02–7.01 (m, 2H), 4.51 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 160.9, 157.9, 150.3, 148.8, 137.9, 131.3, 129.4, 129.2, 128.7, 127.2, 120.9, 120.7, 114.2, 61.9, 55.4, 14.4. Spectral properties were in accordance with the literature.[17]

Ethyl 6-(4-chlorophenyl)-4-phenylpicolinate (4d) White solid; 55% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.08–8.05 (m, 3H), 7.74–7.73 (m, 2H), 7.55–7.47 (m, 5H), 4.52 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 157.1, 150.7, 149.0, 137.6, 137.1, 135.7, 129.6, 129.3, 129.1, 128.6, 127.2, 121.8, 121.2, 62.1, 14.4. Spectral properties were in accordance with the literature.[17]

Ethyl 4-phenyl-6-(*p*-tolyl)picolinate (4e) White solid; 35% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26–8.25 (m, 1H), 8.07–8.02 (m, 3H), 7.75–7.74 (m, 2H), 7.54–7.49 (m, 3H), 7.32–7.30 (m, 2H), 4.52 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 158.3, 150.3, 148.9, 139.6, 137.9, 135.9, 129.6, 129.4, 129.2, 127.2, 127.2, 121.3, 121.2, 61.9, 21.4, 14.4. Spectral properties were in accordance with the literature.[17]

Ethyl 6-phenyl-4-(*p*-tolyl)picolinate (4f) White solid; 59% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.12–8.07 (m, 3H), 7.66–7.65 (m, 2H), 7.52–7.49 (m, 3H), 7.34–7.33 (m, 2H), 4.52 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 158.3, 150.3, 148.9, 139.7, 138.8, 134.8, 130.0, 129.4, 128.8, 127.4, 127.0, 121.3, 121.2, 61.9, 21.3, 14.4. Spectral properties were in accordance with the literature.[17]

Ethyl 4-(4-chlorophenyl)-6-phenylpicolinate (4g) White solid; 43% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.11 (d, J = 7.8 Hz, 2H), 8.05 (s, 1H), 7.69–7.68 (m, 2H), 7.52–7.45 (m, 5H), 4.53 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 158.5, 149.2, 149.1, 138.4, 136.2, 135.8, 129.7, 129.5, 128.9, 128.5, 127.4, 121.3, 62.1, 14.4. Spectral properties were in accordance with the literature.[17]

Ethyl (E)-4-phenyl-6-styrylpicolinate (4h) White solid; 32% yield; mp: 82-85 ℃; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.86 (s, 1H), 8.74–7.70 (m, 3H), 7.63–7.62 (m, 2H), 7.55–7.50 (m, 3H), 7.44–7.39 (m, 3H), 7.34–7.33(m, 1H), 4.54 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 156.7, 150.3, 148.6, 137.5, 136.3, 134.6, 129.6, 129.3, 128.8, 128.8, 127.5, 127.4, 127.2, 122.1, 121.6, 62.2, 14.4; IR (film) 3056, 2982, 1712, 1591, 1445, 1254, 1145, 757; ESI-HRMS $C_{21}H_{18}NO_2$ ($[M+H]^+$): calcd 316.1333, found 316.1331.

2,4,6-Triphenylpyridine (4A) White solid; 14% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, J = 7.8 Hz, 4H), 7.89 (s, 2H), 7.75 (d, J = 7.8 Hz, 2H), 7.55–7.44 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 150.3, 139.5, 139.1, 129.2, 129.1, 129.0, 128.8, 127.2, 127.2, 117.2. Spectral properties were in accordance with the literature.[18]

2,6-Bis(4-methoxyphenyl)-4-phenylpyridine (4B) White solid; 15% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 4H), 7.77 (s, 2H), 7.73–7.72 (m, 2H), 7.53–7.50 (m, 2H), 7.47–7.45 (m, 1H), 7.04–7.02 (m, 4H), 3.88 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 156.9, 150.1, 139.3, 132.2, 129.1, 128.9, 128.4, 127.2, 115.8, 114.0, 55.4. Spectral properties were in accordance with the literature.[18]

2,6-Diphenyl-4-(*p*-tolyl)pyridine (4C) White solid; 18% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, J = 7.8 Hz, 4H), 7.88 (s, 2H), 7.66 (d, J = 7.8 Hz, 2H), 7.53–7.50 (m, 4H), 7.46–7.44 (m, 2H), 7.33 (d, J = 7.8 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 150.2, 139.6, 139.2, 136.1, 129.9, 129.1, 128.7, 127.2, 127.1, 117.0, 21.3. Spectral properties were in accordance with the literature.[18]

4-(4-Chlorophenyl)-2,6-diphenylpyridine (4D) White solid; 12% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ

8.19 (d, J = 7.8 Hz, 4H), 7.83 (s, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.53–7.44 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 149.0, 139.3, 137.5, 135.3, 129.4, 129.2, 128.8, 128.5, 127.2, 116.9. Spectral properties were in accordance with the literature.[18]

ACKNOWLEDGEMENTS

We acknowledge the Key Natural Science Foundation of Anhui Higher Education Institution (KJ2017A446), the Excellent Young Talents Support Program of Anhui Higher Education Institutions (gxgnfx2018035), and the Innovation and Entrepreneurship Project of College Students in Anhui Province (X202110380021).

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15. CCDC 2174552 (**3a**) contains the supplementary crystallo-graphic data for this paper. These data can be obtained free charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
16. CCDC 2174561 (**4d**) contains the supplementary crystallo-graphic data for this paper. These data can be obtained free charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.
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