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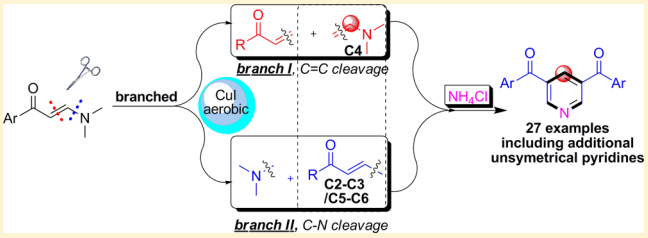
Domino Reactions Involving the Branched C−N and C═C Cleavage of Enaminones Toward Pyridines Synthesis

Jie-Ping Wan,* Youyi Zhou, and Shuo Cao

Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. China

Supporting Information

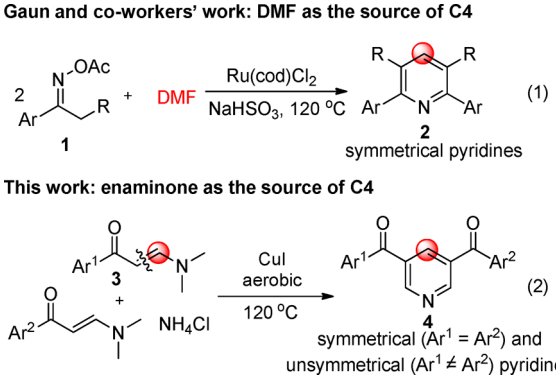
ABSTRACT: The copper-catalyzed cascade reactions of enaminones and ammonium chloride have led to the unprecedented synthesis of 4-unsubstituted pyridines of both symmetrical and unsymmetrical structures. Under the aerobic copper-catalyzed conditions, the branched transformations of enaminones with C−N and C═C bond cleavage provide the C2-C3/C5-C6 and C4 building blocks to construct the pyridine ring, respectively. The C═C cleavage that provides the C4 atom in the pyridine product is the first example showing the reactivity of an enaminone as the donor of one carbon synthon.



The enaminones that contain the O═C-C═C-NR^{1}R^2 backbone have been known as highly reactive and versatile building blocks in organic synthesis.[1] Their applications have been found in the synthesis of numerous organic products of different central backbones, such as heterocycles,[2] benzene aromatics,[3] acyclic molecules,[4] and natural products.[5] According to the available literature on the enaminone-based synthesis, the major reactive sites in enaminones consist of the electrophilic carbon in the carbonyl, the nucleophilic α-carbon and amino group, (R^1 and/or R^2 = H) as well as the easily cleavable active C−N bond (R^1, R^2 ≠ H).[1] Interestingly, as a central fragment in the molecule, the C═C bond has scarcely been found to undergo a transformation in enaminone-based organic synthesis. While the C═C bond is a fundamental organic functional group possessing tremendous reactivity, the highly polar C═C bond in enaminones, as activated by both the electron-donating amino group and the electron-withdrawing carbonyl group, is reasonably of high potential to act as the reactive fragment in enaminone-based reactions. In this context, exploring new reaction pathways by functionalizing the C═C bond is presently an issue of significance in order to expand the frontiers of enaminone chemistry.

A pyridine ring is a fundamental heterocyclic motif showing up in numerous natural products, therapeutic agents, and materials.[6] In addition, as an electron-deficient aromatic system, pyridines have also been well-known as useful organic bases,[7] ligands,[8] as well as central building blocks in a broad array of organic syntheses.[9] Therefore, it is not surprising that the research interest toward the synthesis of pyridines remains highly active and extensive in despite of the long history of pyridine chemistry. Since the discovery of the classical Hantzsch pyridine synthesis by oxidizing 1,4-dihydropyridines,[10] spectacular advances have been achieved in the area of pyridine synthesis, as demonstrated by the reports of numerous alternative synthetic methodologies targeting on this heterocycle. Particularly, in recent years, the pyridine synthesis has received dramatic progress as promoted by the rapid occurrence of many novel synthetic tools and concepts.[11] Among the important strategies for pyridine synthesis, exploring new C4 sources to construct pyridine ring constitutes a critical issue. As a typical example, Guan and co-workers have recently reported the pyridine synthesis using DMF as C4 resource, which leads to the synthesis of a class of useful symmetrical pyridines **2** using ketoxime acetates **1** (eq 1, Scheme 1).[12] Herein, we report a new tactic for pyridine synthesis by employing the assembly of enaminones **3** and ammonium chloride wherein enaminones undergo the branched C−N and C═C bond cleavage to, respectively, provide the C2-C3/C5-C6 and C4 fragments to construct the pyridines **4** (eq 2, Scheme 1). Among the domino transformations, the C═C bond cleavage that provides C4 carbon

Scheme 1. Synthesis of Pyridines with Novel C4 Sources



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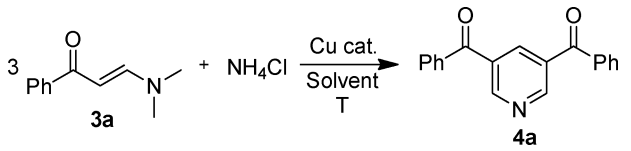
represents a particularly interesting reaction pathway of enaminones. To the best of our knowledge, this is the first time that an enaminone has been found to be capable of donating a single carbon in enaminone-based organic synthesis.

Initially, the titled transformation was observed by subjecting enaminone **3a** with ammonium chloride in the presence of CuBr. Therefore, the reaction between **3a** and ammonium chloride providing pyridine **4a** was systematically investigated to optimize the reaction conditions. First, a class of different Cu(I) and Cu(II) catalysts were employed, respectively. The entries using different copper catalysts, including CuBr, CuCl, CuI, Cu_2O, $Cu(OAc)_2$, CuO, $CuBr_2$, and $CuCl_2$, implied that CuI was the best catalyst by providing **4a** with 85% yield (entries 1–8, Table 1). Subsequently, the variation on the

Table 1. Optimization of Reaction Conditions[a]



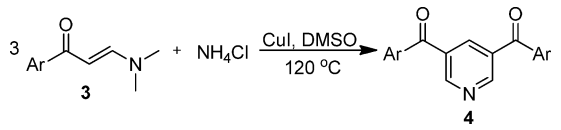
entry	catalyst	solvent	T (°C)	yield (%)[b]
1	CuBr	DMSO	120	81
2	CuCl	DMSO	120	79
3	Cu_2O	DMSO	120	67
4	$Cu(OAc)_2$	DMSO	120	69
5	CuO	DMSO	120	80
6	$CuBr_2$	DMSO	120	75
7	$CuCl_2$	DMSO	120	78
8	CuI	DMSO	120	85
9[c]	CuI	DMSO	120	78
10[d]	CuI	DMSO	120	84
11	CuI	DMSO	110	74
12	CuI	DMSO	130	81
13	CuI	DMF	120	trace
14	CuI	EL	120	17
15[e]	CuI	toluene	120	24
16[e]	CuI	EtOH	120	trace
17[e]	CuI	CH_3CN	120	nr
18[e]	CuI	dioxane	120	nr
19[f]	CuI	DMSO	120	59

[a]Unless otherwise specified, the reaction conditions are **3a** (0.6 mmol), NH_4Cl (0.3 mmol), copper catalyst (0.06 mmol) in 2 mL of solvent(s), stirred for 12 h. [b]Yield of isolated products based on 0.2 mmol of **3a**. [c]The CuI was 0.03 mmol. [d]The CuI was 0.08 mol. [e]The reactions were run at reflux. [f]NH_4OAc was employed as an alternative ammonium source.

loading of CuI showed that 30 mol % was the most appropriate loading (entries 9 and 10, Table 1). In addition, the reaction under both higher and lower temperature did not display improvement in the product yield, either (entries 11 and 12, Table 1). Finally, a class of organic solvents of different polarity, such as DMF, ethyl lactate (EL), toluene, etc., were also subjected, and DMSO turned out to be among the best mediums (entries 13–18, Table 1). Finally, the comparison experiments using different ammonium salts such as NH_4OAc provided a lower yield of product than the entry using NH_4Cl (entry 19, Table 1).

On the basis of the optimized results, the syntheses of different symmetrical pyridines **4** using different enaminone substrates were then conducted. The results from this section were included in Table 2. According to the acquired data, the present protocol was generally applicable for the synthesis of

Table 2. Synthesis of Different Symmetrical Pyridines



entry	Ar	product	yield (%)[a]
1	Ph	**4a**	85
2	4-MeC_6H_4	**4b**	83
3	4-$MeOC_6H_4$	**4c**	72
4	4-$Me_2NC_6H_4$	**4d**	56
5	napth-1-yl	**4e**	77
6	4-ClC_6H_4	**4f**	93
7	4-ClC_6H_4	**4g**	87
8	4-NCC_6H_4	**4h**	62
9	4-$CF_3C_6H_4$	**4i**	77
10	4-$NO_2C_6H_4$	**4j**	84
11	2-MeC_6H_4	**4k**	65
12	3-$MeOC_6H_4$	**4l**	74
13	3,4-$(MeO)_2C_6H_3$	**4m**	62
14	2-BrC_6H_4	**4n**	68
15	3,4-$Cl_2C_6H_3$	**4o**	94
16	3-$NO_2C_6H_4$	**4p**	86
17	thiophene-2-yl	**4q**	91
18	napth-2-yl	**4r**	58

[a]Yield of isolated product based on 0.2 mmol of enaminone **3**.

symmetrical pyridines using aryl functionalized enaminones **3** via their branched transformations. In these entries using enaminones containing a variety of different functional groups, such as alkyl, alkoxyl, halide, nitro, amino, cyano, as well as heteroaryl, the corresponding pyridines were provided with good to excellent yields. Among these entries, the halogenated aryl-based substrates gave excellent yields of related pyridines (**4f**, **4g**, and **4o**, Table 2). However, with the results afforded by the entries using other enaminones of either electron-deficient or enriched structures, the electronic property showed no deducible impact on the reaction results. Another notable point in the results was the synthesis of thiophene-functionalized pyridine **4q**, which proved the good tolerance of the present method to heteroaryl functionalized enaminones. However, when the Ar fragment in enaminones **3** was alternated with an alkyl such as methyl, the target transformation was not observed under the standard conditions. In assigning the product structure, the X-ray single crystal analysis on **4b** was conducted to provide confirmation of pyridine products on the basis of other related spectroscopic analysis.[13]

After the synthesis of symmetrical pyridines **4**, we envisioned that this synthetic method might also be expanded to the synthesis of unsymmetrical pyridines by employing simultaneously two different enaminones. With the tentative attempt, we found that the synthesis of unsymmetrical pyridines was feasible, although related symmetrical pyridines were also isolated as side products. To examine the scope, we then performed expanded experiments of the type by combining enaminones of different properties as substrates. As outlined in Table 3, the entries could generally provide expected unsymmetrical pyridines **5**; however, together with the symmetrical pyridines **4** which were resulted from the homo

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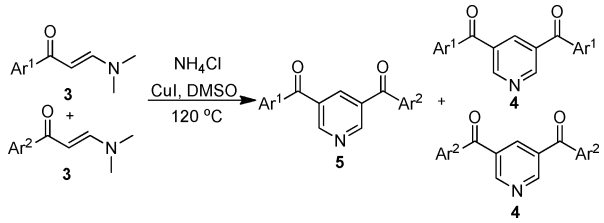
Table 3. Synthesis of Unsymmetrical Pyridines



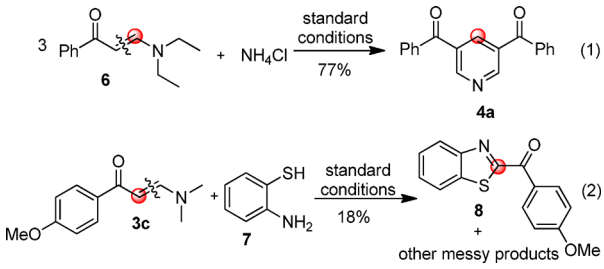
entry	Ar^1	Ar^2	product	yield (%)[a]
1	Ph	4-$MeOC_6H_4$	**5a/4a/4c**	33/26/21
2	4-MeC_6H_4	4-$MeOC_6H_4$	**5b/4b/4c**	36/29/25
3	4-MeC_6H_4	4-$NO_2C_6H_4$	**5c/4b/4j**	38/31/21
4	4-MeC_6H_4	thiophene-2-yl	**5d/4b/4q**	34/36/20
5	4-$CF_3C_6H_4$	4-$NO_2C_6H_4$	**5e/4i/4j**	32/20/28
6	4-$CF_3C_6H_4$	4-NCC_6H_4	**5f/4i/4h**	36/25/24
7	2-MeC_6H_4	3-$NO_2C_6H_4$	**5g/4k/4p**	45/19/28
8	3-$MeOC_6H_4$	3-$NO_2C_6H_4$	**5h/4l/4p**	40/27/23
9	3,4-$Cl_2C_6H_4$	3,4-$(MeO)_2C_6H_4$	**5i/4o/4m**	41/18/24

[a]Yield of isolated product based on 0.2 mmol of **3** (the 2 different enaminones are used in 0.3 mmol + 0.3 mmol; it is assumed that totally 0.2 mmol of enaminone(s) acted as C4 source).

assemblies of both enaminone substrates. In most of these entries, the unsymmetrical pyridines **5** were provided with fair yields that were higher than those of both symmetrical byproducts **4**; an exception was **5d**, which was assembled from the combination of aryl and heteroaryl functionalized enaminones, was isolated with a slightly inferior yield over one of the symmetrical pyridine product 4**b**. The results obtained from these experiments, albeit with relatively lower yields, demonstrated the applicability of the present method for the synthesis of unsymmetrical pyridines.

In order to confirm the branched reaction pathway of enaminones in the present synthesis, we designed control experiments to explore the resource of C4 in pyridine products. As shown in Scheme 2, when *N*,*N*-diethyl functionalized

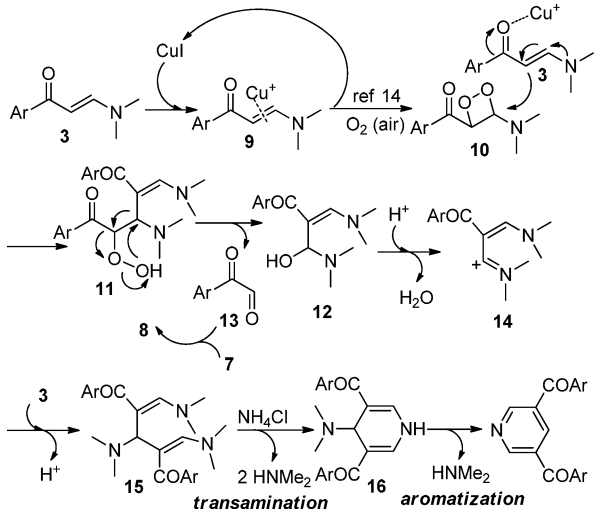
Scheme 2. Control Experiments in Confirming the C4 Source in the Pyridine Products



enaminone **6** was employed as the alternative starting material with NH_4Cl, the pyridine product **4a** was obtained as the only product, demonstrating that the C4 in the product was not provided by the carbon in the *N*-alkyl fragment (eq 1, Scheme 2). In addition, when the enaminone **3c** was subjected with *o*-aminothiophenol **7** to the standard reaction condition, the 2-(*p*-methoxylbenzoyl)benzothiazole **8** could be isolated with 18% yield together with other unknown messy products (eq 2, Scheme 1). This result clearly proved that the C=C bond could be cleaved under the present catalytic conditions and also supported the fact that the C4 fragment in the pyridine was donated by the *β*-carbon in the enaminone, as shown in eq 1.

With the acquired data as well as related literature, we tentatively summarized the mechanism of the reaction. As displayed in Scheme 3, the Cu(I) salt could activate the

Scheme 3. Plausible Mechanism for the Enaminone Branched Synthesis of Pyridines



enaminone to transition state **9**, which could form peroxide intermediates **10** as described in the literaure.[14] The nucleophilic attack of another enaminone to the peroxide ring led to the production of intermediates **11**, and the automatic cleavage of **11** then led to the production of both intermediates **12** and **13**. The intermediates **12**, upon dehydration, provided iminium ion **14**. The subsequent nucleophilic addition of an additional enaminone molecule to **14** produced intermediates **15**, which incorporated ammonium to cyclize via double transamination to give **16**.[15] Finally, the resulting intermediates **16** underwent aromatization to give pyridine products by eliminating dimethylamine.

In conclusion, by employing copper catalysis, we have achieved the synthesis of symmetrical and unsymmetrical pyridines via the simple assemblies of enaminones and ammonium chloride. The main factor that enables the construction of the pyridine ring is the novel branched transformation of enaminones by cleaving both C−N and C=C bonds in this single reaction. The C=C bond cleavage is among the highly interesting since the production of reactive intermediates resulted from this transformation is not only important in the present synthesis but also expected to be useful for the rational design of more novel enaminone-based organic synthesis. Further research in the field is presently ongoing in our group.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Pyridines 4 and 5. In a 25 mL round-bottom flask equipped with a stirring bar were located enaminone(s) **3** (0.6 mmol) or (0.3 + 0.3 mmol, for the synthesis of unsymmetrical pyridines), ammonium chloride (0.3 mmol), CuI (0.06 mmol), and DMSO (2 mL). The vessel was then stirred at 120 °C for 12 h at an air atmosphere. After completion of the reaction (TCL), the mixture was mixed with water (5 mL) and then extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After filtration, the organic solvent was removed from the solution under reduced pressure. The resulting residue was then subjected to silicon chromatography to give pure product by using mixed ethyl acetate/petroleum ether as eluent (v/v = 1/10).

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*3,5-Dibenzoylpyridine (**4a**)*. Yield: 49 mg; 85%; white solid; mp 125−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 2 H), 8.48 (s, 1 H), 7.85 (d, J = 8.0 Hz, 4 H), 7.67 (t, J = 7.2 Hz, 2 H), 7.55 (t, J = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 153.2, 138.1, 136.2, 133.6, 133.0, 130.0, 128.8; IR (KBr, cm^{-1}): 3065, 1660, 1550, 810, 740; ESI-HRMS: Calcd for $C_{19}H_{14}NO_2$ $[M + H]^+$ 288.1025, found: 288.1035.

*3,5-Ditoloylpyridine (**4b**)*. Yield: 52 mg; 83%; gray solid; mp 140−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 2 H), 8.45 (s, 1 H), 7.76 (d, J = 7.6 Hz, 4 H), 7.34 (d, J = 7.6 Hz, 4 H), 2.48 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 152.4, 144.1, 137.4, 133.2, 132.8, 129.8, 129.0, 21.2; IR (KBr, cm^{-1}): 3050, 2900, 1665, 1535, 815; ESI-HRMS: Calcd for $C_{21}H_{18}NO_2$ $[M + H]^+$, 316.1338, found: 316.1346.

*3,5-Di(4-methoxyphenoyl) Pyridine (**4c**)*. Yield: 50 mg; 72%; orange solid; mp 123−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (s, 2 H), 8.39 (s, 1 H), 7.85 (d, J = 8.8 Hz, 4 H), 7.01 (d, J = 8.8 Hz, 4 H), 3.90 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 164.0, 152.6, 137.5, 133.8, 132.6, 129.0, 114.1, 55.6; IR (KBr, cm^{-1}): 3065, 2855, 1670,1550, 790; ESI-HRMS: Calcd for $C_{21}H_{18}NO_4$ $[M + H]^+$, 348.1236, found: 348.1244.

*3,5-Di(4-dimethylaminophenoyl) Pyridine (**4d**)*. Yield: 42 mg; 56%; gray solid; mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 2 H), 8.32 (s, 1 H), 7.79 (d, J = 9.2 Hz, 4 H), 6.69 (d, J = 9.2 Hz, 4 H), 3.10 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 153.8, 151.4, 137.5, 134.6, 132.8, 123.6, 110.8, 40.1; IR (KBr, cm^{-1}): 3050, 2855, 1670, 1535, 810; ESI-HRMS: Calcd for $C_{23}H_{24}N_3O_2$ $[M + H]^+$ 374.1869, found: 374.1876.

*3,5-Di(naphth-1-oyl) Pyridine (**4e**)*. Yield: 60 mg; 77%; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 2 H), 8.59 (s, 1 H), 8.26−8.23 (m, 2 H), 8.03 (d, J = 8.0 Hz, 2 H), 7.93−7.91 (m, 2 H), 7.60 (d, J = 6.8 Hz, 2 H), 7.57−7.55 (m, 4 H), 7.49 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 154.4, 138.5, 134.2, 133.9, 132.9, 130.8, 129.2, 128.7, 128.5, 128.0, 126.9, 125.4, 124.3; IR (KBr, cm^{-1}): 3055, 1670, 1585, 880, 750; ESI-HRMS: Calcd for $C_{27}H_{18}NO_2$ $[M + H]^+$ 388.1338, found: 388.1342.

*3,5-Di(4-chlorophenoyl) Pyridine (**4f**)*. Yield: 66 mg; 93%; orange solid; mp 185−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 2 H), 8.44 (s, 1 H), 7.80 (d, J = 8.8 Hz, 4 H), 7.52 (d, J = 8.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 153.2, 140.3, 137.8, 134.4, 132.9, 131.4, 129.2; IR (KBr, cm^{-1}): 3055, 1670, 1580, 815, 710; ESI-HRMS: Calcd for $C_{19}H_{12}Cl_2NO_2$ $[M + H]^+$ 356.0245, found: 356.0255.

*3,5-Di(4-bromophenoyl) Pyridine (**4g**)*. Yield: 77 mg; 87%; gray solid; mp 201−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 2 H), 8.44 (s, 1 H), 7.73−7.68 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ19 2.7, 153.2, 137.9, 134.8, 132.8, 132.3, 131.4, 129.1; IR (KBr, cm^{-1}): 3055, 1668, 1515, 805, 550; ESI-HRMS: Calcd for $C_{19}H_{12}Br_2NO_2$ $[M + H]^+$ 443.9235, found: 443.9236.

*3,5-Di(4-cyanophenoyl) Pyridine (**4h**)*. Yield: 42 mg; 62%; pale yellow solid; mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 2 H), 8.50 (s, 1 H), 7.95 (d, J = 8.4 Hz, 4 H), 7.88 (s, J = 8.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 153.8, 139.3, 137.9, 132.7, 132.1, 130.2, 117.5, 117.0; IR (KBr, cm^{-1}): 3060, 2250, 1675, 1510, 790; ESI-HRMS: Calcd for $C_{21}H_{12}N_3O_2$ $[M + H]^+$ 338.0930, found: 338.0942.

*3,5-Di(4-trifluoromethylphenoyl) Pyridine (**4i**)*. Yield: 65 mg; 77%; yellow solid; mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 2 H), 8.53 (s, 1 H), 7.95 (d, J = 8.0 Hz, 4 H), 7.83 (d, J = 8.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 153.8, 139.0, 138.0, 135.1, 134.8, 132.4, 130.2, 125.9 (q, J_{C-F} = 3.6 Hz), 124.7 (q, J_{C-F} = 270 Hz); IR (KBr, cm^{-1}): 3060, 1670, 1555, 1250, 815; ESI-HRMS: Calcd for $C_{21}H_{12}F_6NO_2$ $[M + H]^+$ 424.0772, found: 424.0771.

*3,5-Di(4-nitrophenoyl) Pyridine (**4j**)*. Yield: 63 mg; 84%; orange solid; mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 2 H), 8.54 (s, 1 H), 8.42 (d, J = 8.0 Hz, 4 H), 8.02 (d, J = 8.0 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 154.0, 150.6, 140.9, 137.9, 132.1, 130.8, 124.1; IR (KBr, cm^{-1}): 3055, 1670, 1590, 1530, 820; ESI-HRMS: Calcd for $C_{19}H_{12}N_3O_6$ $[M + H]^+$ 378.0726, found: 378.0736.

*3,5-Di(2-methylphenoyl) Pyridine (**4k**)*. Yield: 41 mg; 65%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 2 H), 8.50 (s, 1 H), 7.46 (t, J = 6.8 Hz, 2 H), 7.35 (d, J = 6.4 Hz, 4 H), 7.29 (t, J = 7.6 Hz, 2 H), 2.42 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 154.3, 137.9, 137.8, 136.6, 133.3, 131.7, 131.5, 129.2, 125.6, 20.3; IR (KBr, cm^{-1}): 3050, 2955, 1665, 1550, 810; ESI-HRMS: Calcd for $C_{21}H_{18}NO_2$ $[M + H]^+$ 316.1338, found: 316.1354.

*3,5-Di(3-methoxyphenoyl) Pyridine (**4l**)*. Yield: 51 mg; 74%; pale yellow solid; mp 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 2 H), 8.48 (s, 1 H), 7.45−7.39 (m, 4 H), 7.35 (d, J = 7.6 Hz, 2 H), 7.20 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2 H), 3.88 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 160.0, 153.2, 138.1, 137.5, 133.0, 129.7, 122.8, 120.0, 114.2, 55.5; IR (KBr, cm^{-1}): 3065, 2870, 1665, 1480, 800; ESI-HRMS: Calcd for $C_{21}H_{18}NO_4$ $[M + H]^+$ 348.1236, found: 348.1225.

*3,5-Di(3,4-dimethoxyphenoyl) Pyridine (**4m**)*. Yield: 50 mg; 62%; pink solid; mp 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (s, 2 H), 8.41 (s, 1 H), 7.53 (s, 2 H), 7.38 (d, J = 8.4 Hz, 2 H), 6.93 (d, J = 8.4, 2 H), 3.98 (s, 6 H), 3.97 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 154.0, 152.5, 149.5, 137.6, 133.7, 129.1, 125.8, 111.7, 110.1, 56.2, 56.1; IR (KBr, cm^{-1}): 3065, 2855, 1670, 1535, 810; ESI-HRMS: Calcd for $C_{23}H_{22}NO_6$ $[M + H]^+$ 408.1447, found: 408.1443.

*3,5-Di(2-bromophenoyl) Pyridine (**4n**)*. Yield: 60 mg; 68%; yellow solid; mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 2 H), 8.50 (s, 1 H), 7.68 (d, J = 8.0 Hz, 2 H), 7.51−7.41 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 154.8, 138.9, 137.7, 133.6, 132.3, 130.5, 129.5, 127.8, 119.7; IR (KBr, cm^{-1}): 3050, 1665, 1580, 815, 550; ESI-HRMS: Calcd for $C_{19}H_{12}Br_2NO_2$ $[M + H]^+$ 443.9235, found: 443.9231.

*3,5-Di(3,4-dichlorophenoyl) Pyridine (**4o**)*. Yield: 80 mg; 94%; gray solid; mp 160−162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 2 H), 8.38 (s, 1 H), 8.06 (s, 2 H), 7.87 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.8, 153.0, 137.7, 136.3, 131.8, 131.7, 131.4, 131.1, 129.9; IR (KBr, cm^{-1}): 3065, 1670, 1580, 815, 700; ESI-HRMS: Calcd for $C_{19}H_{10}Cl_4NO_2$ $[M + H]^+$ 423.9466, found: 423.9474.

*3,5-Di(3-nitrophenoyl) Pyridine (**4p**)*. Yield: 65 mg; 86%; yellow solid; mp 175−177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 2 H), 8.54 (d, J = 9.2 Hz, 4 H), 8.43 (s, 1 H), 8.28 (d, J = 7.6 Hz, 2 H), 7.89 (t, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.5, 153.8, 148.4, 138.4, 137.8, 136.4, 132.2, 131.1, 128.0, 124.7; IR (KBr, cm^{-1}): 3055, 1675, 1590, 1530, 820; ESI-HRMS: Calcd for $C_{19}H_{12}N_3O_6$ $[M + H]^+$ 378.0726, found: 378.0731.

*3,5-Dithiophen-2-oylpyridine (**4q**)*. Yield: 54 mg; 91%; brown solid; mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (s, 2 H), 8.58 (s, 1 H), 7.84 (d, J = 4.8 Hz, 2 H), 7.70 (d, J = 3.6 Hz, 2 H), 7.24 (t, J = 4.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.2, 152.4, 142.6, 136.7, 135.8, 135.4, 133.6, 128.6; IR (KBr, cm^{-1}): 3120, 3020, 1665, 1405, 710; ESI-HRMS: Calcd for $C_{15}H_{10}NO_2S_2$ $[M + H]^+$ 300.0153, found: 300.0155.

*3,5-Di(naphth-2-oyl) Pyridine (**4r**)*. Yield: 45 mg, 58%; pale yellow solid; mp 179−181 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.32 (brs, 2 H), 8.62 (s, 1 H), 8.34 (s, 2 H), 8.02−7.94 (m, 8 H), 7.68 (t, 2 H, J = 8.4 Hz), 7.61 (t, 2 H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.9, 153.2, 138.1, 135.7, 133.6, 132.4, 132.3, 129.6, 129.1, 129.0, 127.9, 127.2, 125.5, 125.2; IR (KBr, cm^{-1}): 3050, 1667, 1510, 890, 730; ESI-HRMS: Calcd for $C_{27}H_{18}NO_2$ $[M + H]^+$ 388.1338, found: 388.1332.

*3-Benzoyl-5-(4-methoxyphenoyl) Pyridine (**5a**)*. Yield: 21 mg; 33%; ; pink liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1 H), 9.14 (s, 1 H), 8.44 (s, 1 H), 7.86−7.84 (m, 4 H), 7.66 (t, J = 7.2 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 3.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 192.5, 164.1, 152.9, 152.8, 137.9, 136.3, 133.5, 132.6, 132.2, 130.0, 128.9, 128.8, 114.1, 113.7, 55.6; IR (KBr, cm^{-1}): 3055, 2850, 1670, 1555, 815; ESI-HRMS: Calcd for $C_{20}H_{16}NO_3$ $[M + H]^+$: 318.1130, found: 318.1137.

*3-(p-Toloyl)-5-(4-methoxyphenoyl) Pyridine (**5b**)*. Yield: 24 mg; 36%; orange solid; mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 2 H), 8.42 (s, 1 H), 7.85 (d, J = 8.8 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 2 H), 3.91 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 192.9, 164.5, 153.1, 145.1, 138.2, 134.1, 133.0, 132.6, 130.7, 130.5, 129.9, 129.5, 129.4, 114.5, 56.0, 22.1; IR (KBr, cm^{-1}): 3050, 2890, 2865,

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1675, 825; ESI-HRMS: Calcd for $C_{21}H_{18}NO_3$ $[M + H]^+$: 332.1287, found: 332.1292.

*3-(p-Toloyl)-5-(4-nitrophenoyl) Pyridine (**5c**).* Yield: 26 mg; 38%; orange solid; mp 133−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1 H), 9.17 (s, 1 H), 8.47 (s, 1 H), 8.40 (d, J = 8.8 Hz, 2 H), 8.00 (d, J = 8.8 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 2.48 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 192.3, 154.0, 153.0, 150.4, 144.9, 141.2, 137.9, 133.6, 133.4, 130.8, 130.3, 129.6, 129.5, 124.0, 21.7; IR (KBr, cm^{-1}): 3050, 2890, 1670, 1530, 810; ESI-HRMS: Calcd for $C_{20}H_{15}N_2O_4$ $[M + H]^+$ 347.1032, found: 347.1035.

*3-(p-Toloyl)-5-(thiophen-2-oyl) Pyridine (**5d**).* Yield: 20 mg; 34%; gray solid; mp 114−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1 H), 9.08 (s, 1 H), 8.42 (s, 1 H), 7.73−7.60 (m, 4 H), 7.25 (d, J = 8.0 Hz, 2 H),7.13 (t, J = 4.4 Hz, 1 H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 185.2, 153.1, 52.2, 144.7, 142.6, 137.3, 135.7, 135.4, 133.6, 133.4, 130.3, 129.5, 129.1, 128.5, 21.7; IR (KBr, cm^{-1}): 3130, 3060, 2895, 1665, 810; ESI-HRMS: Calcd for $C_{18}H_{13}NO_2S$ $[M + H]^+$: 308.0745, found: 308.0752.

*3-(4-Trifluoromethylphenoyl)-5-(4-nitrophenoyl) Pyridine (**5e**).* Yield: 26 mg; 32%; pale yellow solid; mp 114−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 2 H), 8.53 (s, 1 H), 8.40 (d, J = 8.4 Hz, 2 H), 8.02 (d, J = 8.0 Hz, 2 H), 7.97 (d, J = 8.0 Hz, 2 H), 7.84 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 192.1, 154.0, 153.7, 150.5, 141.0, 138.9, 137.9, 135.1, 134.8, 132.4, 132.0, 130.8, 130.2, 125.9 (q, J_{C-F} = 3.5 Hz), 124.1, 122.0 (q, J_{C-F} = 127 Hz); IR (KBr, cm^{-1}): 3055, 1670, 1540, 1310, 805; ESI-HRMS: Calcd for $C_{20}H_{12}F_3N_2O_4$ $[M + H]^+$: 401.0749, found: 401.0752.

*3-(4-Cyanophenoyl)-5-(4-trifluoromethylphenoyl) Pyridine (**5f**).* Yield: 27 mg; 36%; pink solid; mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1 H), 9.19 (s, 1 H), 8.51 (s, 1 H), 7.95 (d,d, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 4 H), 7.87 (d, J = 8.4 Hz, 2 H), 7.83 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 192.2, 153.9, 153.7, 139.4, 139.0, 137.9, 135.1, 134.8, 132.7, 132.5, 132.1, 130.2, 130.1, 125.9 (q, J_{C-F} = 3.8 Hz), 124.7 (q, J_{C-F} = 274 Hz) 117.5, 117.0; IR (KBr, cm^{-1}): 3055, 2885, 1665, 1350, 810; ESI-HRMS: Calcd for $C_{21}H_{12}F_3N_2O_2$ $[M + H]^+$: 381.0851, found: 381.0852.

*3-(2-Methylphenoyl)-5-(3-nitrophenoyl) Pyridine (**5g**).* Yield: 31 mg; 45%; pale yellow solid; mp 114−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 2 H), 8.65 (s, 1 H), 8.51 (d, J = 8.0 Hz, 1 H), 8.48 (t, J = 2.0 Hz, 1 H), 8.17 (d, J = 7.2 Hz, 1 H), 7.78 (t, J = 8.0 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.38 (t, J = 8.8 Hz, 2 H), 7.33−7.29 (m, 1 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 191.7, 154.6, 153.5, 148.4, 138.0, 137.8, 137.6, 136.3, 135.2, 133.4, 131.9, 131.8, 131.7, 130.2, 129.2, 127.7, 125.6, 124.6, 20.3; IR (KBr, cm^{-1}): 3065, 2880, 1670, 1540, 815; ESI-HRMS: Calcd for $C_{20}H_{15}N_2O_4$ $[M + H]^+$: 347.1032, found: 347.1036.

*3-(3-Nitrophenoyl)-5-(3-methoxylphenoyl) Pyridine (**5h**).* Yield: 29 mg; 40%; orange solid; mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1 H), 9.19 (s, 1 H), 8.67 (s, 1 H), 8.50 (t, J = 8.4 Hz, 2 H), 8.18 (d, J = 7.2 Hz, 1 H), 7.78 (t, J = 8.0 Hz, 1 H), 7.46−7.34 (m, 3 H), 7.20 (d, J = 8.0 Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 191.7, 160.0, 154.1, 153.1, 148.4, 137.9, 137.7, 137.3, 135.2, 133.2, 131.6, 130.2, 129.8, 127.7, 124.6, 122.8, 120.1, 114.3, 55.6; IR (KBr, cm^{-1}): 3055, 2885, 1670, 1535, 810; ESI-HRMS: Calcd for $C_{20}H_{15}N_2O_5$ $[M + H]^+$, 363.0981, found: 363.0981.

*3-(3,4-Dichlorophenoyl)-5-(3,4-dimethoxylphenoyl) Pyridine (**5i**).* Yield: 34 mg; 41%; pink liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1 H), 9.12 (s, 1 H), 8.40 (s, 1 H), 7.93 (s, 1 H), 7.67−7.60 (m, 2 H), 7.51 (s, 1 H), 7.34 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.1, 191.6, 154.1, 153.3, 152.5, 149.6, 138.3, 137.7, 135.8, 133.9, 133.7, 132.1, 131.7, 131.0, 128.9, 126.4, 125.8, 111.7, 110.1, 56.2, 56.1; IR (KBr, cm^{-1}): 3065, 2880, 1675, 820, 720; ESI-HRMS: Calcd for $C_{21}H_{16}Cl_2NO_4$ $[M + H]^+$ 416.0456, found: 416.0450.

*2-(p-Methoxylbenzoyl)benzothiazole (**8**).*[16] Yield: 10 mg; 18%; white solid;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 2 H, J = 8.0 Hz), 8.22 (d, 1 H, J = 8.0 Hz), 8.00 (d, 1 H, J = 8.0 Hz), 7.59−7.50 (m, 2 H), 7.03 (d, 2 H, J = 8.0 Hz), 3.91 (s, 3 H).

■ ASSOCIATED CONTENT

Supporting Information

General experimental information, copies of ^{1}H and ^{13}C NMR spectra of all products, and CIF file containing crystallographic data of **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wanjieping@jxnu.edu.cn (J.-P.W.).

Notes

The authors declare no competing financial interest.

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