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Synergistic H_4NI–AcOH Catalyzed Oxidation of the C_{sp^3}–H Bonds of Benzylpyridines with Molecular Oxygen

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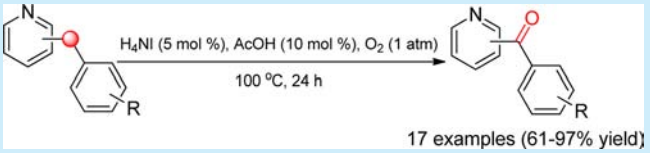
Supporting Information

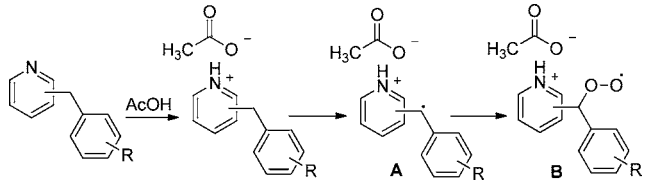
ABSTRACT: The oxidation of benzylpyridines forming benzoylpyridines was achieved based on a synergistic H_4NI–AcOH catalyst and molecular oxygen in high yield under solvent-free conditions. This is the first nonmetallic catalytic system for this oxidation transformation using molecular oxygen as the oxidant. The catalytic system has a wide scope of substrates and excellent chemoselectivity, and this procedure can also be scaled up. The study of a preliminary reaction mechanism demonstrated that the oxidation of the C_{sp^3}–H bonds of benzylpyridines was promoted by the pyridinium salts formed by AcOH and benzylpyridines. The synergistic effect of H_4NI–AcOH was also demonstrated by control experiments.



The direct oxidation of the C_{sp^3}–H bonds is one of the most useful and important transformations in organic chemistry.[1] Benzoylpyridines are very useful intermediates in the synthesis of pharmaceuticals, such as arpromidine, phenirамine, chloropheniramine, triprolidine, doxylamine, etc.[2] The oxidation of the C_{sp^3}–H bonds of benzylpyridines is an attractive way to synthesize benzoylpyridines. Traditionally, stoichiometric quantities of a hazardous oxidant such as potassium permangante were used in this oxidation reaction with large amounts of unwanted byproducts.[3] During recent decades, significant efforts have been made toward the development of oxidative processes to obtain benzoylpyridines from benzylpyridines utilizing transition metals as catalysts.[4] However, the coordination between the N-heterocyclic compound and the transition metal leads to the deactivation of the catalyst and the poor chemoselectivity, and the metal residue is also problematic. Nonmetallic catalysts are preferred to solve the above problems. Although nonmetal-based catalysts have been developed for this oxidation transformation over the past decade, these protocols need a large excess of less sustainable oxidants, such as peroxides.[5] Molecular oxygen is a convenient and green oxidant because water is the only byproduct produced. However, dioxygen is inert.[6] The oxidation of the C_{sp^3}–H bonds of benzylpyridines with nonmetallic catalysts and molecular oxygen remains untouched, and further research in this area is necessary.

A key issue of the oxidation of C_{sp^3}–H bonds of pyridine compounds is its low reactivity owing to the electron-withdrawing N in the pyridine ring. To solve the problem, pyridine *N*-oxides were developed to replace corresponding pyridine compounds initially.[7] In recent years, alternative methods to activate the N-heterocyclic compounds were established. The group of Y. G. Zhou reported that asymmetric hydrogenation of N-heterocyclic compounds could be activated by chloroformates,[8] Brønsted acid,[9] benzyl bromide,[10] etc. Later, A. W. Lei and co-workers reported that the chloroacetate can promote the selective oxidation of heterobenzylic methylenes in the presence of a catalytic amount of copper species using oxygen as the terminal oxidant.[11] We envisioned that a Brønsted acid, for example AcOH, can promote the oxidation of the C_{sp^3}–H bonds of benzylpyridines by forming pyridinium salts (Scheme 1). Another key issue of the oxidation

Scheme 1. Process of the Oxidation of the C_{sp3}–H Bonds of Benzylpyridines with Molecular Oxygen



of C_{sp^3}–H bonds of benzylpyridines with molecular oxygen is the activation of molecular oxygen. In the process of the oxidation of the C_{sp^3}–H bonds of benzylpyridines with molecular oxygen, benzylpyridiniums are changed into corresponding free radical **A**, and then the free radical **A** reacts with O_2 forming the oxygen radical **B** (Scheme 1). So the generation of the free radical **A** is very important for this oxidation reaction. As we know, I_2 is a radical initiator, and iodide can be oxidized to I_2 by molecular oxygen under acid conditions. So we envisioned that iodide, for example KI, can be used in the oxidation of C_{sp^3}–H bonds of benzylpyridines.

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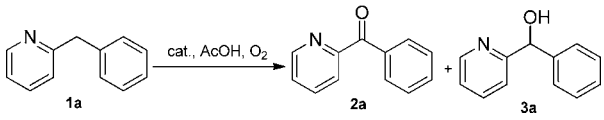
According to the above analysis, we envisioned that the KI−AcOH−O_2 system can carry out the oxidation of 2-benzylpyridine forming 2-benzoylpyridine. We made an attempt to oxidize 2-benzylpyridine (0.5 mmol) with KI (0.5 mmol) and AcOH (0.5 mmol) and O_2 (2 atm) in H_2O (2.5 mL) at 100 °C for 24 h. We obtained the product **2a** in 33% yield and product **3a** in 19% yield (Table 1, entry 1). When we removed AcOH, we detected a trace amount of 2-benzoylpyridine **2a** (Table 1, entry 2). The oxidation reaction could not occur without KI (Table 1, entry 3). KI and AcOH were all necessary to achieve the oxidation reaction. We thought that the hydrolysis of AcOH in H_2O weakens the activation to 2-benzylpyridine and the hydrogen bonds between H_2O solvent or 0.5 mmol AcOH and product **3a** lead to the poor chemoselectivity. So we removed the H_2O solvent and decreased the amount of AcOH to 0.05 mmol. We obtained the product **2a** as the only product in 67% yield (Table 1, entry 4). Next, the type of iodide was studied. When the iodide was chosen, H_4NI, the oxidation reaction gave the best result (Table 1, entries 4−12). Therefore, the H_4NI was selected for the next optimization study. Compared with pure O_2, air which is more easily available and environmentally friendly was chosen as the oxidant, and we also obtained a good result (Table 1, entry 13). Subsequently, we investigated the effect of the pressure of O_2 on the reaction. When the pressure of O_2 was decreased to 1 atm, the result of the oxidation reaction was also excellent (Table 1, entry 14). Next, different amounts of the H_4NI and AcOH were tested, and a 92% isolated yield was obtained when the amount of H_4NI was 5 mol % and the amount of AcOH was 10 mol % (Table 1, entries 15−17). The reaction temperature was also studied. When the temperature was decreased to 80 °C, the yield and chemoselectivity decreased sharply (Table 1, entry 18). We tried to shorten the reaction time, but a poor result was obtained (Table 1, entry 19). The experiment with 5 mol % H_4NI and 10 mol % other acids such as methanesulfonic acid, TFA, and TsOH was performed, and excellent results were obtained (Table 1, entries 20−22). These results suggested that the oxidation reaction could occur smoothly in the presence of other Brønsted acids. At last, we obtained the optimized catalytic system, viz., 5 mol % H_4NI as a catalyst, 10 mol % AcOH as a promoter, and 1 atm of O_2 as an oxidant under solvent-free conditions at 100 °C for 24 h.

Table 1. Optimization of the Reaction Conditions[a]

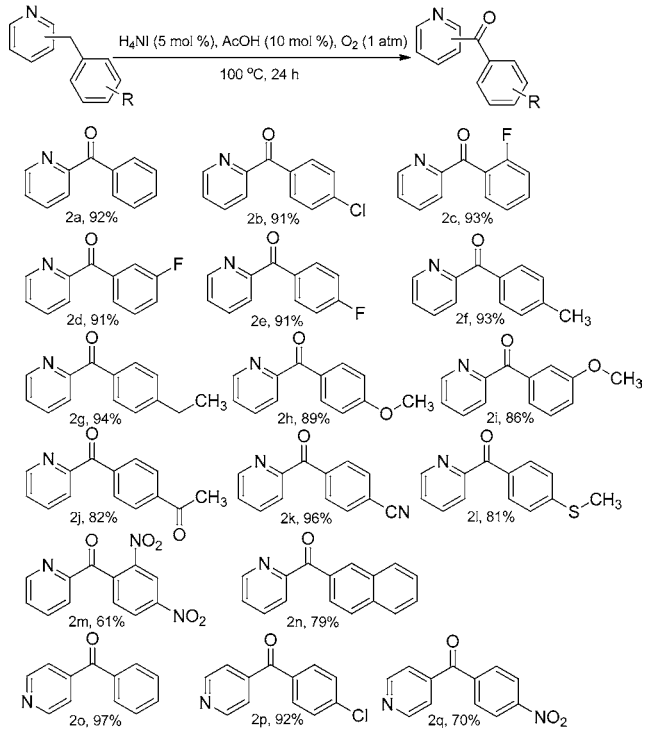


entry	catalyst	additive	solvent	yield[k] (%)
1	KI[b]	AcOH[e]	H_2O	**2a**: 33; **3a**: 19
2	KI[b]	–	H_2O	trace
3	–	AcOH[e]	H_2O	trace
4	KI	AcOH	–	**2a**: 67
5	NaI	AcOH	–	**2a**: 90 (94[l])
6	H_4NI	AcOH	–	**2a**: 93 (96[l])
7	$(CH_3)_4NI$	AcOH	–	**2a**: 15
8	LiI	AcOH	–	**2a**: 68; **3a**: 20
9	ZnI_2	AcOH	–	**2a**: 91 (84[l])
10	AgI	AcOH	–	trace
11	I_2	AcOH	–	**2a**: 89
12	$CH_3(Ph)_3PI$	AcOH	–	**2a**: 79; **3a**: 12
13[g]	H_4NI	AcOH	–	**2a**: 79
14[h]	H_4NI	AcOH	–	**2a**: 93
15[h]	H_4NI[c]	AcOH	–	**2a**: 91 (92[l])
16[h]	H_4NI[d]	AcOH	–	**2a**: 80; **3a**: 9
17[h]	H_4NI[c]	AcOH[f]	–	**2a**: 82; **3a**: 10
18[h,i]	H_4NI[c]	AcOH	–	**2a**: 40; **3a**: 16
19[h,j]	H_4NI[c]	AcOH	–	**2a**: 71; **3a**: 18
20[h]	H_4NI[c]	methanesulfonic acid	–	**2a**: 97
21[h]	H_4NI[c]	TFA	–	**2a**: 92
22[h]	H_4NI[c]	TsOH	–	**2a**: 93

[a]Reaction conditions: **1a** (0.5 mmol), catalyst (10 mol %), AcOH (10 mol %), O_2 (2 atm), 100 °C, 24 h. [b]KI (0.5 mmol). [c]Catalyst (5 mol %). [d]Catalyst (2 mol %). [e]AcOH (0.5 mmol). [f]AcOH (5 mol %). [g]Air (2 atm). [h]O_2 (1 atm). [i]80 °C. [j]16 h. [k]GC-MS yield based on the amount of **1a** used. [l]Isolated yield.

Having identified the optimized reaction conditions, we investigated the scope of the substrates. A variety of substituted 2- or 4-benzylpyridines which have electron-donating and -withdrawing groups in the arene were subjected to our oxidation protocol. The corresponding 2- or 4-benzoylpyridines were obtained in moderate to good yields (Scheme 2, **2a−2q**);

Scheme 2. Scope of Substrates of the Oxidation Protocol (isolated yield)



thus, our oxidation protocol has a wide scope of substrates. *Para*, *meta*, and *ortho* substitution of the arene group was tolerated (Scheme 2, **2c−2e**, **2h−2i**). The substrates that contain two chemically different benzylic positions were tested, and the products **2f** and **2g** were obtained without byproducts in good yields (Scheme 2, **2f**, **2g**). The substrate that contains a thioether group that is sensitive to oxidation was also tested. The thioether group was left untouched, and the corresponding ketone product was obtained in 81% yield (Scheme 2, **2l**). The oxidation protocol showed good chemoselectivity.

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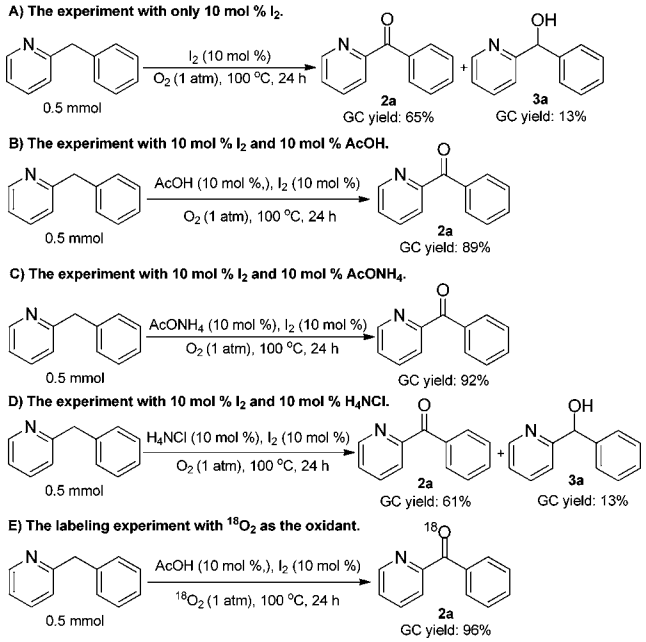
Finally, the practical applicability of the oxidation protocol was demonstrated. We used 2-(4-chlorobenzyl)pyridine as the test substrate and worked on a gram scale. A 25 mmol (5.1 g) reaction of 2-(4-chlorobenzyl)pyridine was performed with 5 mol % of H_4NI as the catalyst, 10 mol % AcOH as the promoter, and 6 atm O_2 as the oxidant at 100 °C. The desired product was obtained in 87% isolated yield within 96 h. This result suggested that our oxidation protocol is a highly active, selective, and practical process for the preparation of (4-chlorophenyl)(pyridin-2-yl)methanone **2b**.

To gain an insight into the mechanism for the oxidation of 2-benzylpyridine to 2-benzoylpyridine, several control experiments were performed. We thought that I_2 was generated in situ from the catalyst. So the experiment with 10 mol % I_2 was performed, and the 2-benzoylpyridine **2a** was obtained in 65% yield with poor chemoselectivity (Scheme 3A). Next, we

Scheme 3. Control Experiments



performed the experiment with 10 mol % I_2 and 10 mol % AcOH, and an excellent result was obtained (Scheme 3B). H_4NI was used in our optimized conditions, so we envisioned that $AcONH_4$ was produced in the oxidation process. The experiment with 10 mol % I_2 and 10 mol % $AcONH_4$ was performed, and the 2-benzoylpyridine **2a** was obtained in 92% yield (Scheme 3C). The oxidation reaction was promoted by AcOH resulting from the hydrolysis (the byproduct of O_2 is H_2O) of AcO^-. For comparison, when we changed the $AcONH_4$ to H_4NCl, the same poor result was obtained with the experiment with only 10 mol % I_2 (Scheme 3D). We performed a labeling experiment with $^{18}O_2$ as the oxidant, and the ^{18}O-labeled product **2a** was obtained in 96% yield (Scheme 3E). This result demonstrated that the carbonyl oxygen atom of the phenyl(pyridin-2-yl)methanone **2a** originated from dioxygen.

To confirm an organic radical species involved in the overall process, electron paramagnetic resonance (EPR) experiments were performed. When H_4NI and AcOH were tested, no signals were observed. The EPR spectrum of a mixture of 2-benzylpyridine, H_4NI, and AcOH displayed a resonance characteristic of an organic radical with an absorption maximum at g = 2.0026 (Figure 1). These EPR results demonstrated the participation of organic radicals in our oxidation reaction system.

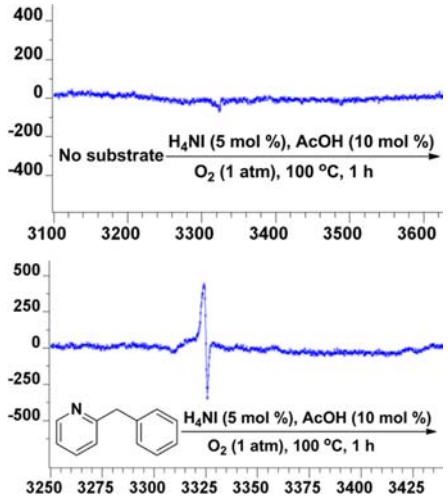
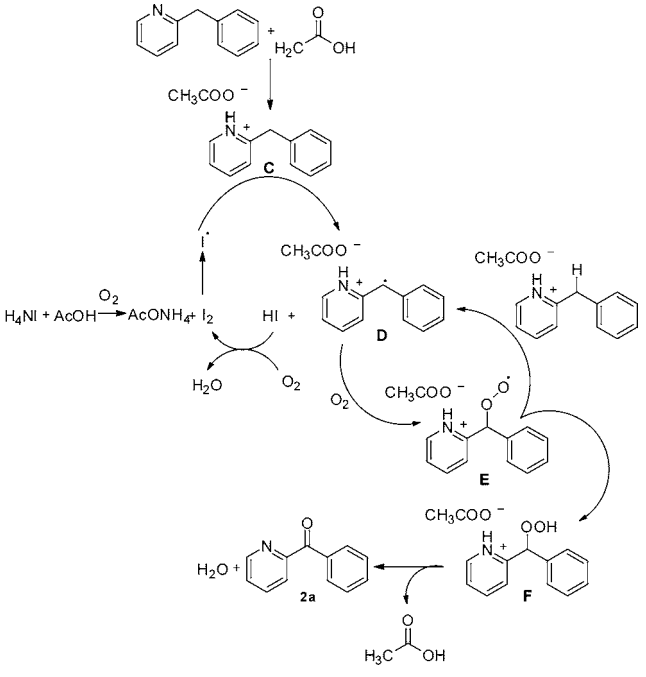


Figure 1. Eelectron paramagnetic resonance (EPR) spectra (X band, 9.3 GHz, 99.1 K).

On the basis of the above results and pertinent literature, we proposed a possible reaction pathway (Scheme 4). Initially, 2-

Scheme 4. Possible Reaction Pathway



benzylpyridinium acetate **C** was formed by interaction between the 2-benzylpyridine and AcOH, and the H_4NI and AcOH were oxidized to $AcONH_4$ and I_2. Then the 2-benzylpyridinium **C** reacted with a iodine radical which was produced from I_2 at high temperature forming free radical **D** and HI which was oxidized to I_2 again. The free radical **D** captured O_2 forming the free radical **E**, and then the free radical **E** reacted with another 2-benzylpyridinium acetate **C** forming intermediate **F** and free radical **D**. The decomposition of intermediate **F** can afford

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product **2a** and released an AcOH molecule. The 2-benzylpyridinium acetate **C** was detected at m/z values of 229.1 with a clear spectrum by GC-MS.

In summary, we have reported for the first time that a nonmetallic catalytic oxidation protocol of the C_{sp^3}–H bonds of benzylpyridines formed benzoylpyridine with the synergistic H_4NI–AcOH catalyst and molecular oxygen. AcOH promoted this oxidation reaction by forming pyridinium salts. This catalytic oxidation protocol has wide substrate scope and excellent chemoselectivity, and this procedure can also be scaled up. No organic solvent is needed in the oxidation process, making it more environmentally friendly. Further studies will be aimed at extending the substrate scope and further investigating the reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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