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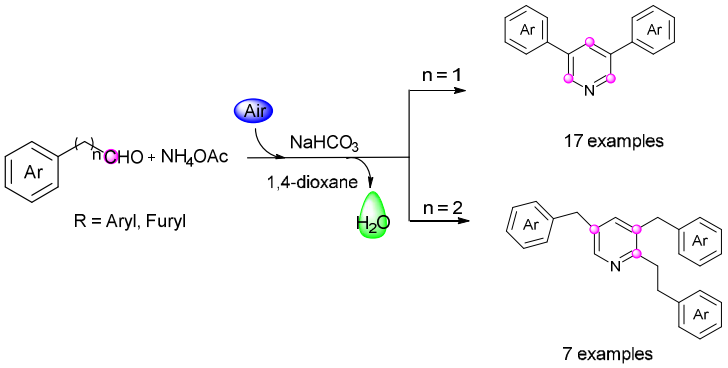

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ARTICLE TYPE

Metal-free Synthesis of Substituted Pyridines from aldehydes and NH_4OAc under Air

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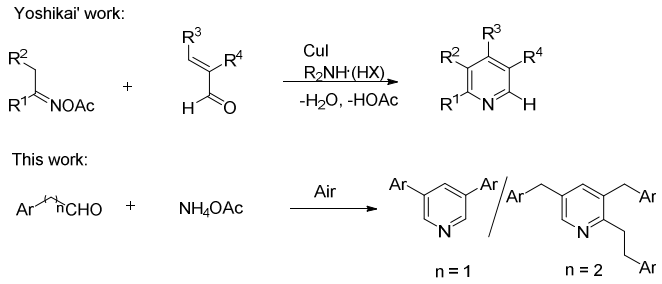
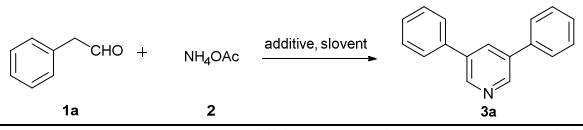
A metal-free and efficient method for the synthesis of substituted pyridines with aldehydes and NH_4OAc under mild conditions using air as the oxidant was developed. This oxidative cyclization process involves direct C-H bond functionalization, C-C/C-N bonds formation and C-C bond cleavage.

Substituted pyridines as one of the most prevalent heterocyclic compounds are important building blocks for many natural products, bioactive molecules, and functional materials,[1] For example, many herbicides and fungicides as well as thousands of drugs contain the skeleton of pyridines.[2] Thus, they have drawn considerable interest for synthetic chemists. Accordingly, numerous of well-documented traditional and modern methods have been developed for the construction of pyridines and their derivatives, among which the tradition metal catalyzed cycloaddition reactions represent as typical method for pyridines synthesis.[3] Especially, the group of Eliel had reported the synthesis of substituted pyridines from aldehyde and ammonia gas via abnormal Chichibabin reaction.[4] Very recently, Yoshikai group has developed syntheses of pyridines from oximes and



Scheme 1 Aldehydes and anilines in the synthesis of pyridines

Table 1 Optimization of reaction condition [a]



1a 2 3a

Entry	N source	Additive	Solvent	Temp	Yield [b]
1	NH_4OAc		DMSO	120	72
2	NH_4HCO_3		DMSO	120	68
3	NH_4Cl		DMSO	120	42
4	$NH_3·H_2O$		DMSO	120	75
5	$(NH_4)_2C_2O_4$		DMSO	120	66
6	$NH_2OH·HCl$		DMSO	120	0
7	NH_4OAc	K_2CO_3	DMSO	120	72
8	NH_4OAc	$NaHCO_3$	DMSO	120	76
9	NH_4OAc	NaOAc	DMSO	120	69
10	NH_4OAc	HOAc	DMSO	120	44
11	NH_4OAc	$NaHCO_3$	DMF	120	75
12	NH_4OAc	$NaHCO_3$	PhMe	100	58
13	NH_4OAc	$NaHCO_3$	EtOH	70	67
14	**NH_4OAc**	**$NaHCO_3$**	**1,4-dioxane**	**90**	**80**
15[c]	NH_4OAc	$NaHCO_3$	1,4-dioxane	90	63
16	NH_4OAc	$NaHCO_3$	H_2O	90	21

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), additive (0.3 mmol), solvent (1 mL), 5h. [b] Yields of isolated products. [c] The reaction was carried out under O_2 (1 atm).

enals (scheme 1).[5] However, most of those methods suffer from several disadvantages such as use of highly toxic metal compounds, instability of the substrates, poor yields and harsh reaction conditions. Therefore, the development of an alternative metal-free approach for the synthesis of pyridines under air remains highly desirable.

Recently, the C-H activation and C-C/C-N bond formation have presented an attractive and powerful strategies for generation heteroaromatic compounds.[6] In view of green and sustainable chemistry, development of economical and

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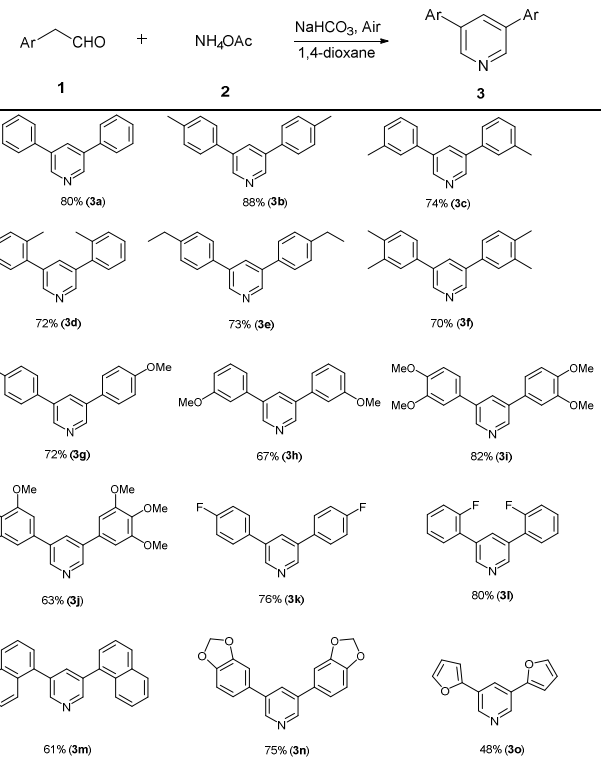
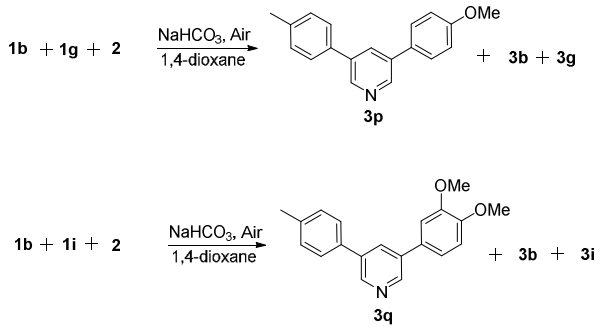
Table 2 Synthesis of pyridines by aldehydes and NH_4OAc [a]



[a] All the reaction were carried out in the presence of **1** (0.3 mmol), **2** (0.9 mmol) and $NaHCO_3$ (0.3 mmol) in 1 mL 1,4-dioxane at 90 °C for 5 h.

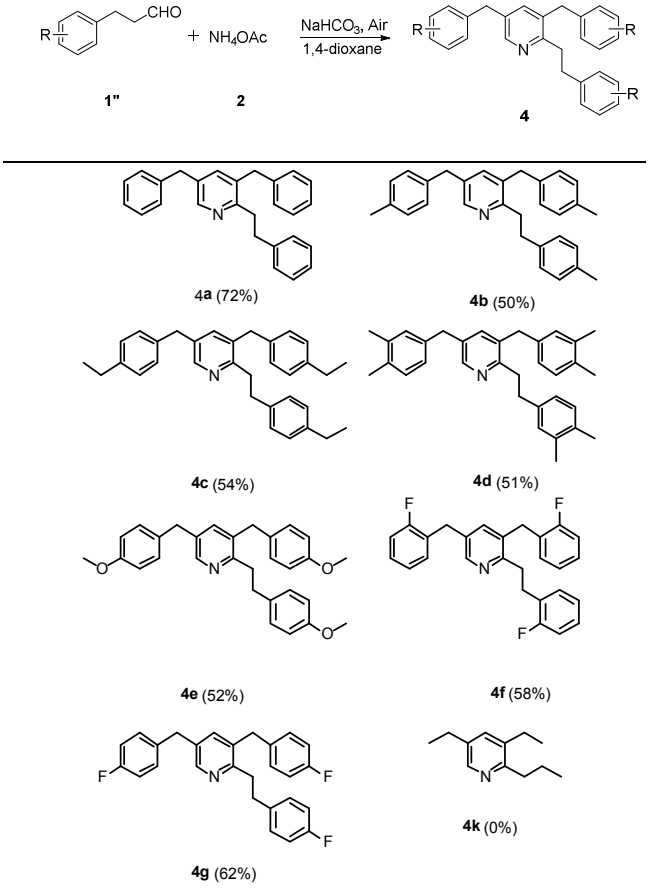
environmentally benign strategies for the construction of useful heterocyclic skeletons with simple and readily accessible substrates is an attractive goal in contemporary organic synthesis. Particularly, air has emerged as an ideal oxidant for the synthesis of heterocyclic compounds in a step and atom-economical fashion for its abundance, environment-friendly and numerous advantages in industry.[7] During our investigation the synthesis of heterocyclic compounds using dioxygen as the oxidant,[8] we discovered a rather surprising formation of substituted pyridines from 2-phenylacetaldehydes and ammonium acetate under air.



Scheme 2 Diversity of polysubstituted pyridines synthesis

In our initial experiments, 2-phenylacetaldehyde (**1a**) and NH_4OAc (**2**) were chosen as the model substrates for the reaction, as shown in Table 1. Treating the substrate **1a** and **2** in DMSO at 120 °C, to our delight, an interesting product 3, 5-

Table 3. Synthesis of 2,3,5-trisubstituted pyridines by substituted 3-phenylpropanal and NH_4OAc



diphenylpyridine (**3a**) was obtained in 72% yield, and we confirmed the structure of **3a** unambiguously through an X-ray crystal analysis. Among the N-source we examined, NH_4OAc was found the best substrate for the reaction (Table 1, entries 1 – 6). Further studies showed that $NaHCO_3$ was the most efficient additive for the reaction when DMSO was used as solvent, affording the desired product in 76% yield (Table 1, entries 7 – 10). After screening on different parameters, the highest yield of **3a** was achieved, when the reaction was carried out at 90 °C in 1, 4-dioxane (Table 1, entry 14).

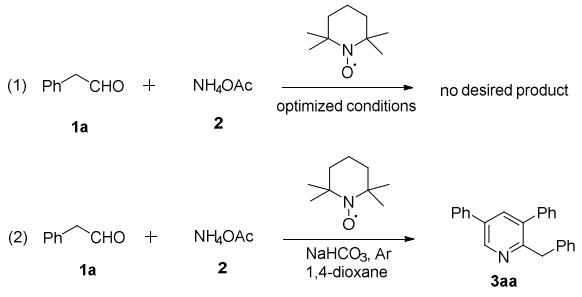
With the optimized reaction conditions in hand, we explored the substrate scope of this reaction, and the results are illustrated in Tables 2. Generally, the reaction of substituted aldehydes and NH_4OAc proceeded smoothly and afforded the corresponding substituted pyridines with high efficiency (Table 2). It is observed that the nature of the substituent on the aromatic rings did not significantly affect the efficiency on the yields of the products. The *ortho*-, *meta*-, and *para*-substituted alkyl groups, as well as the electron-donating and electron-withdrawing groups were well tolerated, such as methyl, methoxyl, fluoro groups (**3a-3n**). The 3,5-di(naphthalen-1-yl)pyridine **3m** was obtained in 61% yield when 2-(naphthalen-2-yl)acetaldehyde 1m was employed as the

substrate. Moreover, when 2-(furan-2-yl) acetaldehyde was subjected to the transformation, the desired product also was obtained in 48% yield (**3o**).

Moreover, different aldehydes also can work together under the optimized conditions, and the scope was further expanded (scheme 2). The reaction of **1b** with **1g** afforded **3p** in 34% yield, and **1b** with **1i** afforded **3q** in 36% yield, respectively. Meanwhile, the **3b**, **3g** and **3i** were also detected in this transformation.

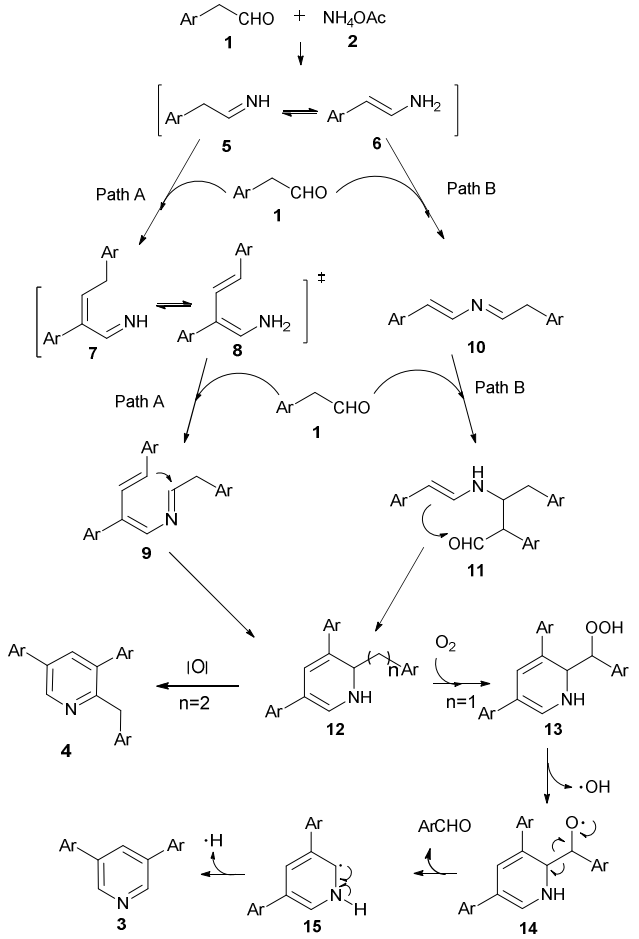
Further experiments were conducted for the reaction of substituted 3-phenylpropanal and NH_4OAc under optimized conditions. As shown in Table 3, the nature of substituted groups on 3-phenylpropanals can not significantly affect this transformation. The substrates with electron-donating and electron-drawing group all can proceed well under the optimized conditions and give the desired products in moderate yields (**4a**-**4g**). However, the reaction did not work when the butyraldehyde were employed as the reaction substrates (**4k**).

To probe the mechanism further, some experiments were investigated. Firstly, annulation of **1a** and **2** was carried out under standard conditions, benzaldehyde was detected by GC-MS in the reaction system. The radical traping experiment was also performed in the presence of 2,2,6,6-teramethylpiperidine oxide (TEMPO). Indeed, the addition of 2.0 equiv of TEMPO that led to the oxidative process was remarkly suppressed and no desired porduct and usful intermediate was iolated (Scheme 3, step 1). Fortunately, When 2.0 equiv of TEMPO was employed in this transformation via standard condition under argon, an unexpected compound 2-benzyl-3,5-diphenylpyridine (**3aa**) was detected (Scheme 3, step 2). The structure of product **3aa** and **4** mean that the carbon atom of C-2 position in pyridine ring comes from the carbonyl of aldehydes in this transformation. Moreover, the product of **3aa** indicates that **12** would be the intermediate of the transformation.



Scheme 3 Control experiments

On the basis of the results described above, a plausible mechanism with two paths is proposed in Scheme 4. First, the acetaldehyde **1** condenses with **2** to form imine **5**, which would proceed aldol condensation with **1** to afford **7**. The intermediate **7** equilibrates to generate enamine **8** easily.[9] Then, intermediate **12** is formed via intramolecular nucleophile addition from imine **9**, which is generated by the reaction of enamine **8** and **1** (Path A). Alternatively, the imine **5** also can equilibrate to generate the enamine **6**. Sequently, the intermediate **10** is formed by the reaction of enamine **6** and **1**. Intermolecular nucleophile addition of **10** and **1** gives rise to **11** (Path B). Then, **12** is generated by the intramolecular nucleophile. Furthermore, when substituted 3-phenylpropanals were served as substrates, the hydroperoxide **12** was converted to product **4** via the hydride elimination directly. When substituted acetaldehyde



Scheme 4 Proposed mechanism of the synthesis pyridines

were served as substrates, the hydroperoxide **13** is provided by the combination of the intermediate **12** and O_2. Moreover, the radical **14** and hydroxide radical (•OH) are generated by decomposition of the hydro peroxide **13**. The single electron transfer of **14** forms the radical **15** and aldehyde with C-C cleavage. Finally, the pyridine **3** is afforded by the radical hydride elimination of **15**.

In conclusion, we have developed a simple and efficient method for the synthesis of substituted pyridines. This method constructs the skeleton of pyridine with aldehydes and NH_4OAc by direct C-H functionalization, C-C/C-N bond formation and C-C bond cleavage under mild reaction conditions. The procedure, using air as oxidative agent, is a very practical, economical, and environmentally friendly protocol for the synthesis of substituted pyridines. This work was supported by National Natural Science Foundation of China (21202067) and the Fundamental Research Funds for the Central Universities (lzujbky-2014-71).

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