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Iron-Catalyzed Cyclization of Ketoxime Carboxylates and Tertiary Anilines for the Synthesis of Pyridines

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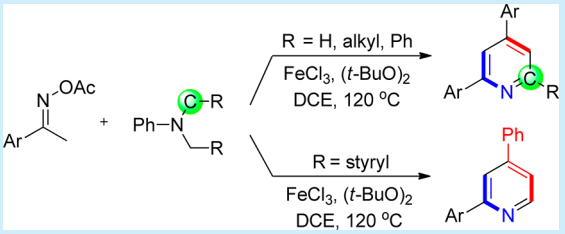
Supporting Information

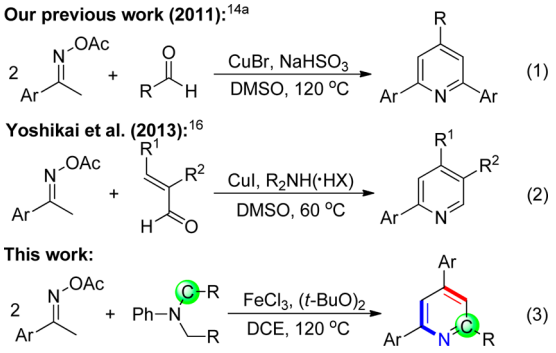
ABSTRACT: A novel and efficient iron-catalyzed cyclization of ketoxime carboxylates and *N*,*N*-dialkylanilines for the modular synthesis of diverse pyridines was developed. The reaction was initiated by Fe-catalyzed N−O bond cleavage of ketoxime carboxylates in the presence of tertiary anilines. The methylene carbon on *N*,*N*-dialkylanilines functioned as a source of one-carbon synthon in the reaction. The reaction used readily available starting materials, tolerated various functional groups, and afforded 2,4-disubstituted and 2,4,6-trisubstituted pyridines in good to high yields under mild conditions.



Pyridines represent an important class of heterocycles and are ubiquitous scaffolds in medicinal chemistry, natural products, functional materials, and agrochemistry.[1] Consequently, much effort has been devoted to the development of synthetic methods to access these useful pyridines.[2,3] In the past decades, diverse formal [3 + 3]-,[4] [4 + 2]-,[5] [2 + 2 + 2]-cycloadditions[6] and cycloisomerizations[7] toward the pyridine core have been developed. Many valuable substituted pyridines were synthesized by these methods. However, versatile aryl-substituted pyridines are still one of the most challenging compounds. Since the importance of aryl-substituted pyridines in organic synthesis has been established, a concise and flexible method for the synthesis of aryl-substituted pyridines is highly desirable.

Ketoximes and derivatives are readily available chemicals. However, the chemistry of ketoximes was less developed in traditional organic synthesis.[8] In the past decade, transition-metal-catalyzed transformations of ketoximes have been paid extensive close attention. Narasaka−Heck amination with ketoximes has been developed by Narasaka and co-workers.[9] Pd(0)-catalyzed cyclization of ketoxime carboxylates has also been developed by the groups of Abell,[10] Zhu,[11] Hartwig,[12] and Bower.[13] Cu-catalyzed coupling reactions of ketoxime carboxylates has been developed by our[14] and other groups.[15] In 2011, we developed the first Cu-catalyzed condensation of ketoxime acetates and aldehydes for the synthesis of symmetrical pyridines (Scheme 1, eq 1).[14a] Subsequently, Cu/iminium-co-catalyzed condensation of ketoxime acetates and α,β-unsaturated aldehydes for the synthesis of 2,4-di- or 2,3,4-trisubstituted pyridines was developed by Yoshikai and co-workers (Scheme 1, eq 2).[16] Despite these advances, the development of novel mode for transition-metal-catalyzed transformation of ketoximes for the synthesis of useful structures is still highly desirable.[17] Recently, Fe-catalyzed oxidative methylenation of 1,3-dicarbonyl compounds using *N*,*N*-dimethylaniline as methylene donor has been developed by Li and co-workers.[18b,c] Fe-catalyzed acylation of indoles using secondary anilines as the carbonyl source has been developed by Su and Wu.[18d] We hypothesized that environmentally friendly and abundant iron salts may prompt the N−O bond cleavage of the ketoxime carboxylate, thus implying that Fe-catalyzed coupling of ketoximes and the α-C(sp^3)−H bond of tertiary amines may occur. Interestingly, the Fe-catalyzed reaction of ketoxime acetates and tertiary anilines directly gave aryl-substituted pyridines. In this paper, we describe the development of an unprecedented Fe-catalyzed cyclization of ketoxime carboxylates and tertiary anilines for the synthesis of diverse pyridines (Scheme 1, eq 3). The methylene carbon on *N*,*N*-dialkylanilines functioned as a source of one-carbon synthon in the reaction.

Scheme 1. Transition-Metal-Catalyzed Synthesis of Pyridines from Ketoxime Carboxylates



We began our study with the Fe-catalyzed reaction of acetophenone oxime acetate **1a** and *N*,*N*-dimethylaniline **2a**. Gratifyingly, when $FeCl_2$ was used as the catalyst, 2,4-diphenylpyridine **3aa** was observed in 18% yield in toluene at

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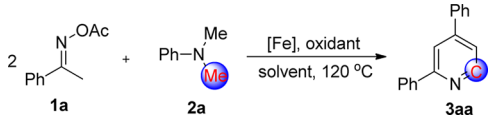
120 °C (Table 1, entry 1). The 2,4-diphenylpyridine product should come from the cyclization of two molecules of

Table 1. Optimization of the Reaction Conditions[a]



entry	[Fe]	oxidant	solvent	temp (°C)	yield (%)
1	$FeCl_2$		toluene	120	18
2	$FeCl_2$	O_2	toluene	120	22
3	$FeCl_2$	TBHP[b]	toluene	120	16
4	$FeCl_2$	H_2O_2[c]	toluene	120	0
5	$FeCl_2$	DTBP	toluene	120	52
6	$FeCl_3$	DTBP	toluene	120	60
7	$Fe(OTf)_2$	DTBP	toluene	120	26
8	$Fe(OTf)_3$	DTBP	toluene	120	20
9		DTBP	toluene	120	0
10	$FeCl_3$	DTBP	1,4-dioxane	120	16
11	$FeCl_3$	DTBP	CH_3CN	120	74
12	**$FeCl_3$**	**DTBP**	**DCE**	**120**	**86**(68)[d]
13	$FeCl_3$		DCE	120	37
14	$FeCl_3$	DTBP	DCE	100	62
15	$FeCl_3$	DTBP	DCE	140	80

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), [Fe] (10 mol %), oxidant (0.6 mmol), solvent (3 mL), 5 h, in air; isolated yields. [b]TBHP (5–6 M in decane). [c]30 wt % solution in water. [d]Reaction was performed under argon.

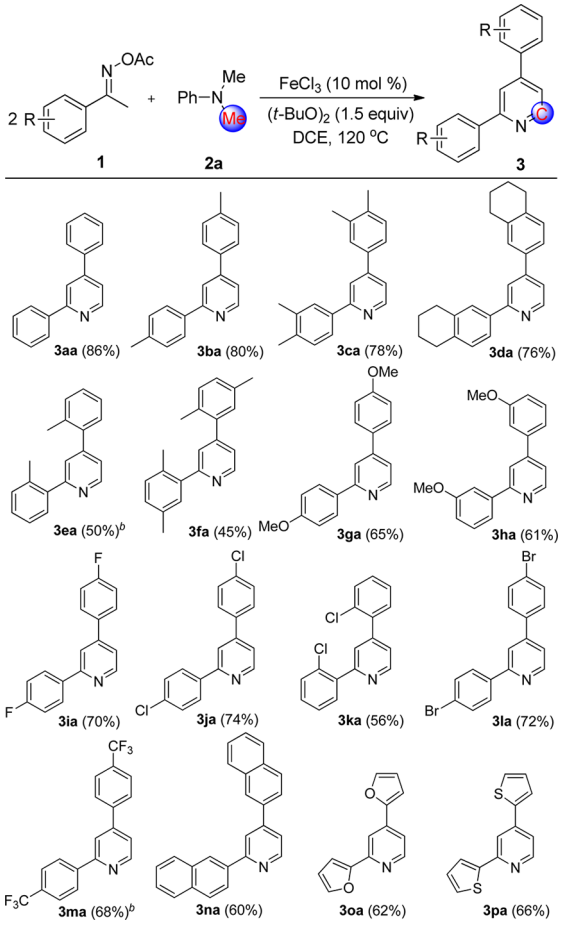
acetophenone oxime acetate **1a** and a methyl group on *N*,*N*-dimethylaniline **2a**. The reaction indicated that N–O bond cleavage of the ketoxime acetates occurred in the presence of Fe catalyst and tertiary anilines. This interesting primary result prompted us to optimize the reaction conditions to develop an Fe-catalyzed reaction of ketoxime acetates and tertiary anilines for the synthesis of substituted pyridines.

Various oxidants such as O_2, *tert*-butyl hydroperoxide (TBHP), H_2O_2, and di-*tert*-butyl peroxide (DTBP) were then screened to optimize the reaction (Table 1, entries 2–5). DTBP was found to be the most effective oxidant, providing **3aa** in 52% yield. Further experiments showed that $FeCl_3$ was superior to $FeCl_2$ (Table 1, entry 6). Other iron catalyst precursors such as $Fe(OTf)_2$ and $Fe(OTf)_3$ were less reactive in the reaction (Table 1, entries 7 and 8). Notably, no reaction occurred in the absence of the iron catalyst or in the presence of copper catalyst,[19] indicating that the iron catalyst is essential for the reaction (Table 1, entry 9). Next, various solvents such as 1,4-dioxane, CH_3CN, and DCE were screened (Table 1, entries 10–12). DCE was found to be the optimal solvent for the reaction, affording pyridine **3aa** in 86% yield (Table 1, entry 12). Notably, the 2,4-diphenylpyridine **3aa** was obtained in 68% yield when the reaction was performed under argon, and the 2,4-diphenylpyridine **3aa** was observed in 37% yield in absence of the DTBP under air (Table 1, entry 13). These results indicate that oxygen combined with DTBP acted as the oxidant in the reaction. Moreover, the reaction temperature was also varied. The optimum temperature for the reaction was found to be 120 °C (Table 1, entries 14 and 15).

To evaluate the potential of amines to function as a source of one-carbon synthon, various tertiary and secondary amines were investigated under the standard conditions (see Scheme S1). The reaction of acetophenone oxime acetate **1a** with 4-methyl-*N*,*N*-dimethylaniline **2b** affords the desired pyridine **3aa** in 74% yield, whereas electron-withdrawing (−Br, −CN) groups on aniline decreased the yield of **3aa**. These results clearly indicate that the choice of amines is crucial for the reaction. Subsequently, different acetophenone oxime carboxylates were investigated to test their reactivity. These results indicate that the carboxylate group at the ketoximes has little effect on the cyclization reaction (see Scheme S2).

With the optimized reaction conditions in hand, the scope of the reaction was investigated (Scheme 2). This novel Fe-

Scheme 2. Fe-Catalyzed Cyclization of Ketoxime Acetates and *N*,*N*-Dimethylaniline[a]



[a]Reaction conditions: **1** (0.4 mmol), **2a** (0.4 mmol), $FeCl_3$ (10 mol %), $(t\text{-BuO})_2$ (0.6 mmol, 1.5 equiv), DCE (3 mL), in air; isolated yields. [b]CH_3CN was used as solvent.

catalyzed cyclization reaction exhibited good functional-group tolerance and proved to be a general method for the facile construction of 2,4-disubstituted pyridines. Ketoxime acetates with electron-neutral or electron-donating groups on aryl rings such as methyl, alkyl, and methoxyl afforded the corresponding 2,4-diarylpyridines **3ba–da,ga–ha** in good yields (61–80%).[20] Ketoxime acetates with electron-withdrawing substituents, such as fluoro, chloro, and bromo, were well tolerated and afforded the corresponding 2,4-diarylpyridines **3ia–ja,la** in 70–74% yields. Moreover, trifluoromethyl-substituted ketoxime acetate proceeded smoothly to afford the desired 2,4-di(4-(trifluoromethyl)phenyl)pyridine **3ma** in 68% yield in CH_3CN.[21] These results indicated that the electronic nature of

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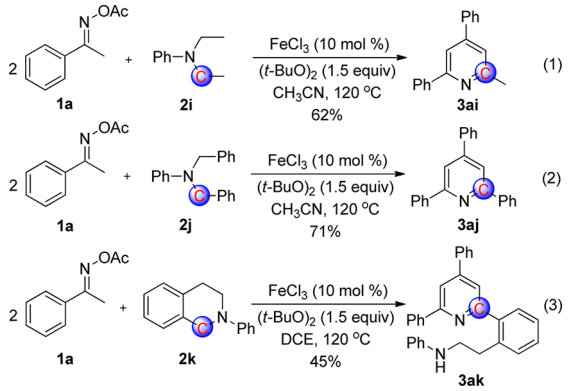
the ketoxime acetates has little effect on the reaction. However, the steric effect plays a role in the reaction. *o*-Methyl- or chloro-substituted ketoxime acetates afforded the desired 2,4-diarylpyridines **3ea**−**fa**,**ka** in moderate yields. In addition, *β*-naphthyl methyl ketoxime acetate **1n**, furanyl methyl ketoxime acetate **1o**, and thiophene-2-yl methyl ketoxime acetate **1p** also reacted well to give the desired 2,4-disubstituted pyridines **3na**−**pa** in 60−66% yields, respectively. However, no reaction occurred when an aliphatic ketoxime acetate such as 3,3-dimethylbutan-2-one oxime acetate was employed as the substrate.

On the basis of the aforementioned results, it was expected that 2,4,6-trisubstituted pyridines could be synthesized by using alternative *N*,*N*-dialkylanilines. Expectedly, 6-methyl-2,4-diphenylpyridine **3ai** was obtained in 62% yield in the presence of *N*,*N*-diethylaniline **2i** (Scheme 3, eq 1). 2,4,6-Triphenylpyridine **3aj**

Scheme 3. Construction of 2,4,6-Trisubstituted Pyridine by Using Alternative *N*,*N*-Dialkylanilines

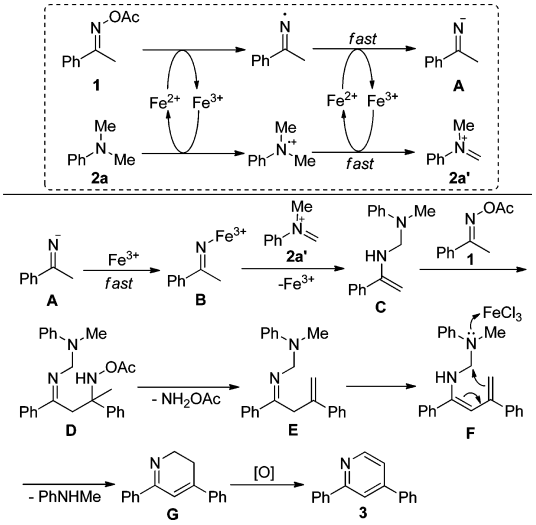


was also obtained in 71% yield when *N*,*N*-dibenzylaniline **2j** was used as the substrate (Scheme 3, eq 2). These results also reveal that the carbon at the 6-position of pyridine product **3** definitely comes from the methylene carbon on the *N*,*N*-dialkylaniline **2**.

To study the byproduct in the dealkylation of *N*,*N*-dialkylanilines, the cyclization of acetophenone oxime acetate **1a** and *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **2k** was performed under the standard reaction conditions (Scheme 3, eq 3). In this reaction, *N*-(2-(4,6-diphenylpyridin-2-yl)phenethyl)-aniline **3ak** was obtained in 45% yield, clearly indicating that the dealkylation of *N*,*N*-dialkylanilines produced *N*-alkylaniline species in the reaction.

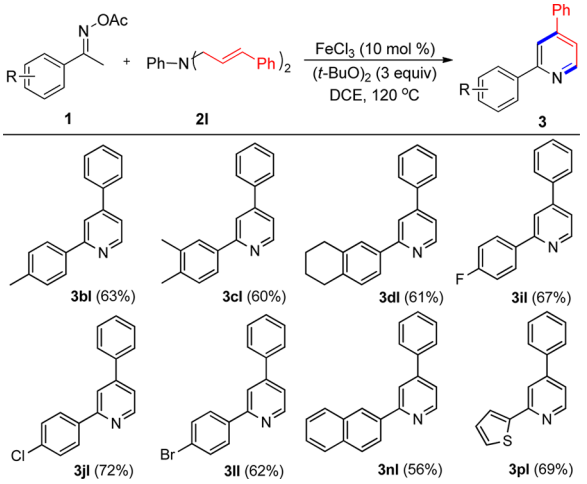
On the basis of the above results,[22] a tentative mechanism for the Fe-catalyzed cyclization is proposed, as shown in Scheme 4. The first step of the reaction is the reduction of Fe^{3+} by *N*,*N*-dimethylaniline **2a** to afford Fe^{2+} species and iminium ion intermediate **2a′**.[23] Then, reductive cleavage of the N−O bond of ketoxime acetate **1** by Fe^{2+} species via a two-step single electron-transfer process forms the imine anion intermediate **A** and Fe^{3+} species. Rapid coordination of intermediate **A** and Fe^{3+} species gives the imino−Fe^{3+} intermediate **B**. Next, nucleophilic addition of **B** to iminium ion intermediate **2a′** produces the enamine intermediate **C**. Addition of enamine intermediate **C** to a second molecular of ketoxime acetate **1** gives the intermediate **D** followed by the release of NH_2OAc to afford the intermediate **E**.[14] Tautomerization of **E** gives intermediate **F**, and intramolecular deamination cyclization of the intermediate **F** assisted by $FeCl_3$ forms the intermediate **G**. Finally, oxidative aromatization of intermediate **G** produces the 2,4-diarylpyridine **3**.

Scheme 4. Tentative Mechanisms for Fe-Catalyzed Cyclization of Ketoxime Acetates and Tertiary Anilines



In the above reaction, the 2,4-diarylpyridines with identical aryls were synthesized. To extend the flexibility of the reaction, Fe-catalyzed cycloaddition of ketoxime acetate **1a** and *N*,*N*-dicinnamylaniline **2l** was conducted under the above conditions. Delightfully, the desired 2,4-diphenylpyridine **3aa** was obtained in 66% yield. Inspired by this result, we synthesized a series of 2,4-diarylpyridines with different aryls by this method using different ketoxime acetates (Scheme 5). Notably, the procedure

Scheme 5. Fe-Catalyzed Cyclization of Ketoxime Acetates and Dicinnamylaniline[a]



[a]Reaction conditions: **1** (0.2 mmol), **2l** (0.24 mmol), $FeCl_3$ (10 mol %), $(t\text{-BuO})_2$ (0.6 mmol), DCE (3 mL), in air; isolated yields.

shows a good method for the synthesis of 2,4-diarylpyridines with different aryls. Ketoxime acetates with methyl, alkyl, fluoro, chloro, and bromo on the aromatic ring gave the corresponding 2,4-diarylpyridines **3bl**−**ll** in 60−72% yields, indicating that the reaction was insensitive to the electronic nature of the ketoxime acetates. *β*-Naphthyl-substituted ketoxime acetate **1n** proceeded smoothly as well to give the corresponding 2-(naphthalen-2-yl)-4-phenylpyridine **3nl** in 56% yield. In addition, a heterocyclic ketoxime acetate such as **1p** was also tolerated and afforded the desired 4-phenyl-2-(thiophene-2-yl)pyridine **3pl** in 69% yield.

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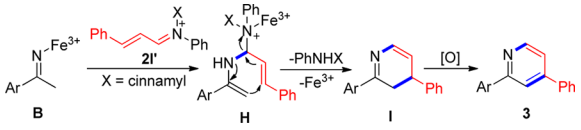
The mechanism proposed for the reaction is illustrated in Scheme 6. Nucleophilic addition of intermediate **B** to the

Scheme 6. Proposed Mechanism for the Synthesis of Pyridines with Different Aryls



iminium ion **2l′** affords intermediate **H**. The intramolecular cyclization/deamination of intermediate **H** gives the intermediate **I**. Finally, oxidative aromatization of **I** produces the 2,4-diarylpyridine **3**.

In conclusion, we have developed an unprecedented Fe-catalyzed cyclization of ketoxime carboxylates and *N,N*-dialkylanilines for the synthesis of 2,4-disubstituted and 2,4,6-trisubstituted pyridines. It is a novel reaction for Fe-catalyzed N–O bond cleavage of the ketoxime carboxylates in the presence of tertiary anilines. The methylene carbon on *N,N*-dialkylanilines functioned as a source of one-carbon synthon in the reaction. The catalytic system was allowed to extend to cyclization of ketoxime carboxylates and *N,N*-dicinnamylaniline for the synthesis of 2,4-diarylpyridines with different aryls. These methods show good procedures for rapid elaboration of the readily available ketoxime carboxylates into diverse valuable substituted pyridines in high yields under mild reaction conditions. Further study of the scope and mechanism is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00326.

Detailed experimental procedures, characterization data, and copies of NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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(19) No reaction occurred when a variety of copper catalysts such as CuI, CuBr, CuCl, $CuBr_2$, $CuCl_2$, and $Cu(OAc)_2$ were screened in the reaction.

(20) The byproduct of the reaction was the corresponding ketone.

(21) All of the reactions listed in Scheme 2 were performed both in DCE and CH_3CN. DCE gave better yields in most cases, but CH_3CN gave better result for **3ea** and **3ma**.

(22) Fe-catalyzed three-component cyclization of ketoxime acetate, ketone (or *N*-Ts-protected ketoimine), and *N,N*-dimethylaniline under the standard conditions was not successful; see the Supporting Information. This result indicated that the ketone is not an intermediate in the reaction.

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