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Ruthenium-Catalyzed Cyclization of Ketoxime Acetates with DMF for Synthesis of Symmetrical Pyridines

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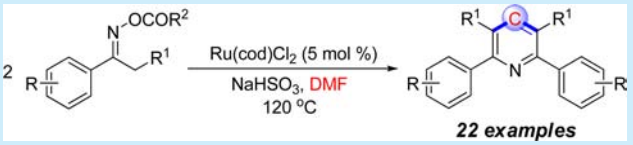
Supporting Information

ABSTRACT: A novel ruthenium-catalyzed cyclization of ketoxime carboxylates with *N,N*-dimethylformamide (DMF) for the synthesis of tetrasubstituted symmetrical pyridines has been developed. A methyl carbon on DMF performed as a source of a one carbon synthon. And $NaHSO_3$ plays a role in the reaction.



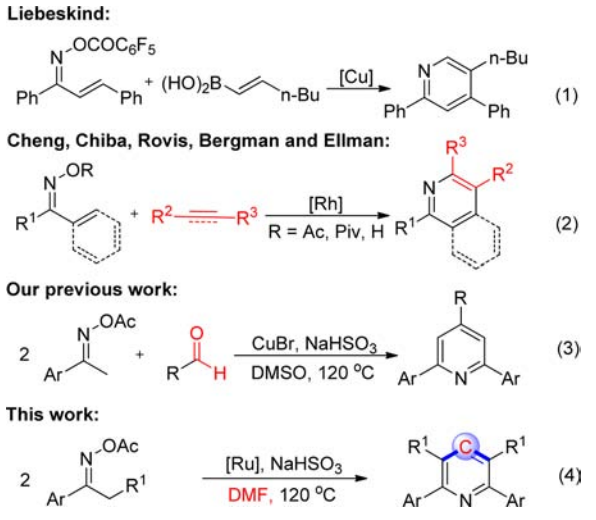
Pyridines represent an important class of hererocycles which are prevalent in natural products, functional materials, and medicinal chemistry.[1] Particularly, a number of symmetrical pyridines have been discovered to have good biological activity.[2] Over the past decades, various methods, such as condensation of amines and carbonyl compounds,[3] transition-metal-catalyzed cycloaddition reactions,[4] and cycloisomerization reactions[5] have been established for the synthesis of pyridines. However, these methods are mainly focused on versatile unsymmetrical substituted pyridines;[6] a general protocol for the synthesis of valuable symmetrical pyridines has rarely been developed.[7]

Recently, transition-metal-catalyzed coupling of ketoxime carboxylates with alkenylboronic acids, alkynes, or alkenes has emerged as a straightforward method to synthesize substituted pyridines,[8] in which the N−O bond cleavage of the ketoxime carboxylates acts as an internal oxidant to make the reactions proceed under mild redox-neutral conditions (Scheme 1, eqs 1 and 2). Inspired by some of these works, we have developed an efficient copper-catalyzed cyclization of ketoxime acetates with aldehydes for the synthesis of symmetrical pyridines (Scheme 1, eq 3).[9a] However, the reaction is mainly limited in the synthesis of 2,4,6-trisubstituted symmetrical pyridines.

DMF is a popular polar solvent. Recently, DMF has been employed as a promising reactant in organic transformations such as formylation,[10] amination,[11] and cyanation reactions.[12] Insertion of arynes into the C═O bond of DMF has been discovered in multicomponent reactions.[13] Very recently, a Rh-catalyzed direct α-methylation of ketones by DMF has also been disclosed.[14] However, to our knowledge, employing DMF as a source of a one carbon synthon to perform a cyclization reaction has rarely been reported.[15] In this paper, we have developed a novel and efficient ruthenium-catalyzed cyclization of ketoxime carboxylates with DMF for the synthesis of 2,3,5,6-tetrasubstituted symmetrical pyridines (Scheme 1, eq 4).

When we studied reactions of propiophenone oxime acetate **1a** in DMF, an unexpected 3,5-dimethyl-2,6-diphenylpyridine **2a** was observed in 9% yield in the presence of the $[Ru(p\text{-cymene})Cl_2]_2$ catalyst (Table 1, entry 1). The symmetrical

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



pyridine formation reveals that DMF may undergo the cyclization reaction with propiophenone oxime acetate **1a** acting as a carbon source. This interesting result encouraged us to optimize the reaction conditions to provide a general protocol for the synthesis of tetrasubstituted symmetrical pyridines which are less accessible by traditional methods.

Therefore, various additives were screened to examine if they could improve the reaction efficiency. Similar to our previous finding in the copper-catalyzed reaction of ketoximes,[9] $NaHSO_3$ could dramatically improve the yield of pyridine **2a** to 60%. Other additives, such as Na_2SO_3 and $Na_2S_2O_4$, were inferior to $NaHSO_3$ (Table 1, entries 2−4). Optimizing with various ruthenium catalysts, such as $Ru(acac)_3$, $RuCl_3$, $Ru(cod)Cl_2$, and $Ru_3(CO)_{12}$, revealed that $Ru(cod)Cl_2$ was the

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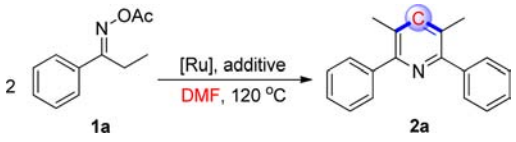
Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	[Ru] catalyst	additive	t (°C)	yield (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$	–	120	9
2	$[Ru(p\text{-cymene})Cl_2]_2$	Na_2SO_3	120	16
3	$[Ru(p\text{-cymene})Cl_2]_2$	$Na_2S_2O_4$	120	22
4	$[Ru(p\text{-cymene})Cl_2]_2$	$NaHSO_3$	120	60
5	$Ru(acac)_3$	$NaHSO_3$	120	35
6	$RuCl_3 \cdot xH_2O$	$NaHSO_3$	120	51
7	$Ru(cod)Cl_2$	$NaHSO_3$	120	73
8	$Ru_3(CO)_{12}$	$NaHSO_3$	120	53
9	–	$NaHSO_3$	120	0
10	$Ru(cod)Cl_2$	$NaHSO_3$	140	72
11	$Ru(cod)Cl_2$	$NaHSO_3$	100	26

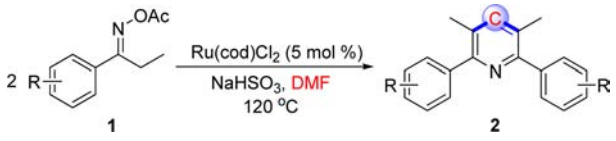
[a]Reaction conditions: **1a** (0.4 mmol), catalyst (5 mol %), additive (1.5 equiv), DMF (2 mL), 5 h, in air; isolated yields.

most effective catalyst for this reaction, improving the yield of **2a** to 73% (Table 1, entries 5−8). Additionally, no reaction occurred in the absence of a ruthenium catalyst, thus indicating that a ruthenium catalyst is essential for this reaction (Table 1, entry 9). Furthermore, the reaction temperature was also varied; the experiments show that the optimal temperature for the reaction is 120 °C (Table 1, entries 10−11).

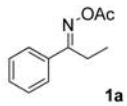
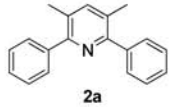
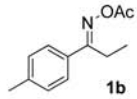
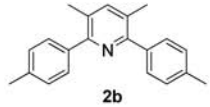
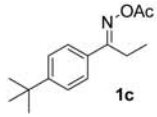
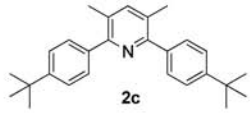
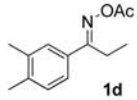
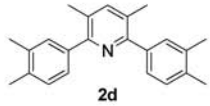
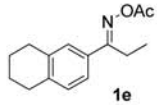
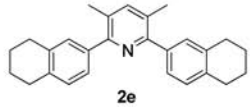
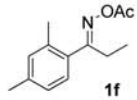
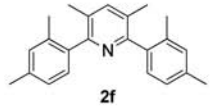
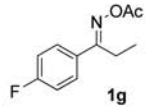
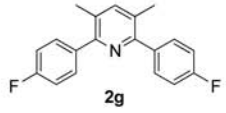
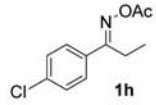
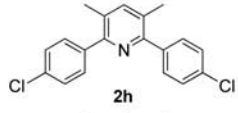
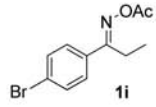
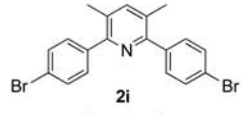
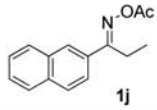
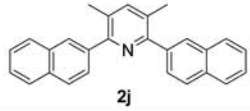
With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). This transformation proved to be a general method for the preparation of tetrasubstituted symmetrical pyridines. Propiophenone oxime acetates with electron-donating or -withdrawing groups on aryl rings, such as methyl, *tert*-butyl, fluoro, chloro, and bromo, all gave the corresponding symmetrical pyridines **2b−2i** in good yields, thus implying that the electronic nature of the substrates has little influence on the reaction (Table 2, entries 1−9). However, the steric effect plays a role in the reaction. The desired symmetrical pyridine **2f** was obtained only in 24% yield when *ortho*-methyl substituted propiophenone oxime acetate **1f** was employed as the substrate (Table 2, entry 6). In addition, the 1-(naphthalen-2-yl)propan-1-one oxime acetate **1j** also reacted smoothly to give the desired naphthyl substituted symmetrical pyridine **2j** in 68% yield (Table 2, entry 10).

Next, a series of phenyl alkyl ketoxime acetates were investigated to extend the substrate scope (Table 3). Ketoxime acetates derived from butyrophenone, valerophenone, and α-tetralone reacted smoothly to give the desired symmetrical pyridines **2k−2m** in moderate to good yields (Table 3, entries 1−3). Tetraphenylpyridine **2n** was also obtained in 50% yield when 1,2-diphenylethanone oxime acetate **1n** was used as the substrate (Table 3, entry 4). Notably, the corresponding ketone was observed as the main byproduct in the above reactions. Furthermore, acetophenone oxime acetates which may provide 2,6-disubstituted symmetrical pyridines were studied as the substrates. Expectedly, 2,6-diarylpyridines **2o−2q** were afforded in reasonable yields under standard conditions (Table 3, entry 5). However, the 2,6-dithienylpyridine **2r** was obtained in only 30% yield (Table 3, entry 6). And no reaction occurred when (*E*)-1-(pyridin-2-yl)ethanone oxime acetate **1s** or butan-2-one oxime acetate **1t** was employed as the substrates (Table 3,

Table 2. Ru-Catalyzed Cyclization of Aryl Ethyl Ketoxime Acetates with DMF[a]



1 2

entry	substrate	product	yield (%)
1	 1a	 2a	73
2	 1b	 2b	77
3	 1c	 2c	71
4	 1d	 2d	72
5	 1e	 2e	70
6	 1f	 2f	24
7	 1g	 2g	67
8	 1h	 2h	76
9	 1i	 2i	72
10	 1j	 2j	68

[a]Reaction conditions: **1** (0.4 mmol), $Ru(cod)Cl_2$ (5 mol %), $NaHSO_3$ (1.5 equiv), DMF (2 mL), 120 °C, in air; isolated yields.

entries 7−8). It should be noted that different propiophenone oxime carboxylates, such as propionate, *tert*-butyrate, and benzoate, with the exception of pentafluorobenzoate, show similar reactivity to that of acetate (Table 3, entries 9−12).

To gain insight into the reaction mechanism, a deuterium labeling experiment was carried out. The reaction became considerably slower under the conditions to afford 4-deuterated pyridine **2o** in 30% yield when DMF-d_7 was used as the solvent (Scheme 2, eq 5). This result confirmed that the carbon on the 4-position of the pyridine ring should indeed come from DMF.

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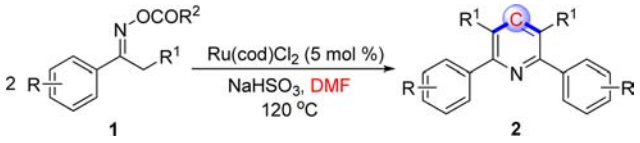
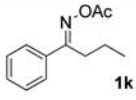
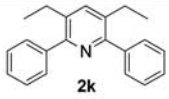
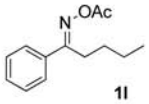
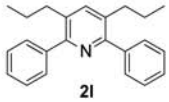
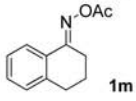
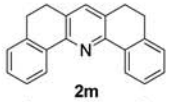
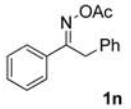
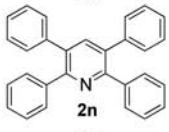
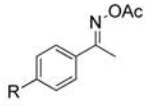
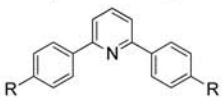
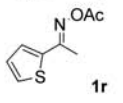
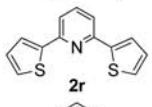
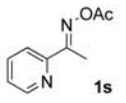
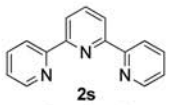
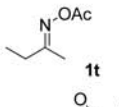
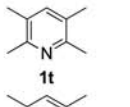
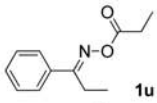
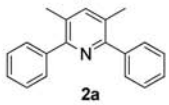
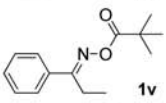
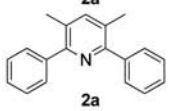
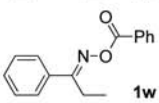
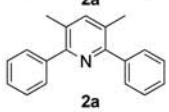
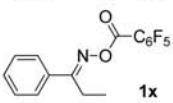
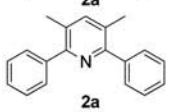
Table 3. Ru-Catalyzed Cyclization of Various Ketoxime Carboxylates with DMF[a]

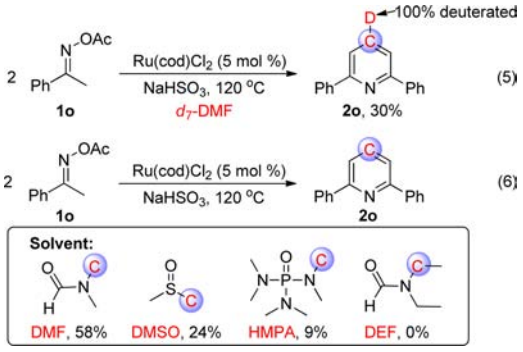


entry	substrate	product	yield (%)
1	 1k	 2k	68
2	 1l	 2l	60
3	 1m	 2m	46
4	 1n	 2n	50
5	 **1o** (R=H) **1p** (R=Me) **1q** (R=Cl)	 **2o** (R=H) **2p** (R=Me) **2q** (R=Cl)	58 62 56
6	 1r	 2r	30
7	 1s	 2s	0
8	 1t	 1t	0
9	 1u	 2a	66
10	 1v	 2a	62
11	 1w	 2a	53
12	 1x	 2a	<5

[a]Reaction conditions: **1** (0.4 mmol), $Ru(cod)Cl_2$ (5 mol %), $NaHSO_3$ (1.5 equiv), DMF (2 mL), 120 °C, in air; isolated yields.

Further, the reaction occurred as well when DMSO or hexamethylphosphoramide (HMPA) was used as the solvent albeit in low yield. However, the reaction did not occur when *N,N*-diethylformamide was employed (Scheme 2, eq 6). These

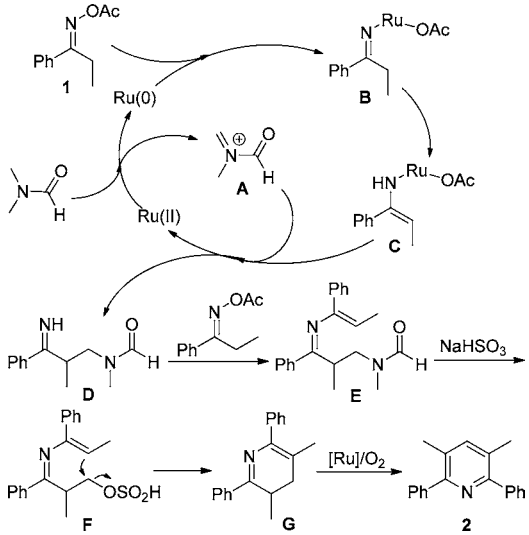
Scheme 2. Investigation of the Reaction Mechanism



results indicate that the carbon unit should be provided by a methyl carbon on DMF.

On the basis of the aforementioned results and previous studies, a tentative mechanism for the reaction is proposed in Scheme 3. Oxidation of DMF by Ru(II) gives an iminium

Scheme 3. A Tentative Mechanism for Ru-Catalyzed Cyclization of Ketoxime Carboxylates with DMF



species **A** and Ru(0).[12] Subsequently, oxidative addition of ketoxime acetate **1** to Ru(0) generates an imino-Ru(II) complex **B**, which undergoes tautomerization to afford an enamino-Ru(II) complex **C**.[9] Then, nucleophilic addition of **C** to species **A** produces an imine intermediate **D**. Condensation of imine intermediate **D** with a second ketoxime acetate **1** gives an intermediate **E**.[9] Nucleophilic substitution of **E** by $NaHSO_3$ followed by intramolecular cyclization of the intermediate **F** forms a dihydropyridine intermediate **G**. Finally, Ru-catalyzed oxidative aromatization of intermediate **G** in the presence oxygen generates the desired pyridine product **2**. Alternatively, nucleophilic substitution by the $NaHSO_3$ step could occur prior to the condensation.

In summary, we have developed a novel Ru-catalyzed cyclization of ketoxime carboxylates with DMF for the synthesis of tetrasubstituted symmetrical pyridines. A methyl carbon on DMF performed as a source of a one carbon synthon in the reaction. The reaction is a good protocol for the rapid elaboration of readily available ketoxime acetates into a variety of valuable tetrasubstituted symmetrical pyridines under mild

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conditions. Further study on the transition-metal-catalyzed transformations of ketoxime carboxylates are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all products. 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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