

Copper-Catalyzed Coupling of Oxime Acetates with Aldehydes: A New Strategy for Synthesis of Pyridines

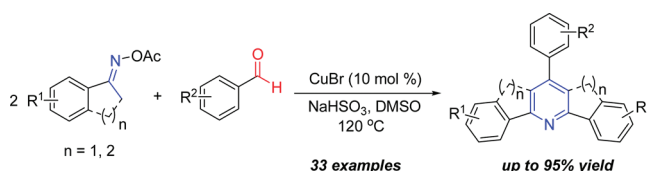
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Received August 24, 2011

ABSTRACT



Copper-catalyzed coupling of oxime acetates with aldehydes offers a new strategy for the synthesis of highly substituted pyridines. This novel method tolerates a wide range of functionality and allows for rapid elaboration of the oxime acetates into a variety of substituted pyridines.

Oximes and their derivatives are valuable synthetic building blocks.¹ They are well-known fruitful candidates for the Beckmann rearrangement reactions to prepare amides² or for the dehydration reactions to produce nitriles.³ Recently, transition metal catalyzed coupling reactions using oximes and their derivatives as substrates have emerged. Coupling of oximes with aryl halides or arylboronic acids have been used for construction of the synthetic useful *O*-arylhydroxylamines.⁴ Alternatively,

attractive elegant strategies for the coupling of oxime carboxylates with boronic acids (eq 1),⁵ arynes (eq 2),⁶ or aromatic C–H bonds (eq 3)⁷ were recently explored for efficient construction of a series of aza-heterocycles (Scheme 1). Cleavage of the N–O bond in oxime carboxylates by a low valent transition metal, such as Pd(0) and Cu(I), shows a new promising approach to nitrogen-containing compounds. Despite these advances, the development of new methodologies for transition metal catalyzed coupling of the electrophilic oxime carboxylates with alternative electrophiles remains largely unrealized. The challenges of the reactions include the following: (1) cleavage of the N–O bond in oxime carboxylates involves two pathways: oxidative addition and radical process; (2) coupling of two electrophiles is subject to an efficient reducing agent in the reaction system.

Substituted pyridines are one of the most prevalent heterocycles in many natural products, pharmaceuticals,

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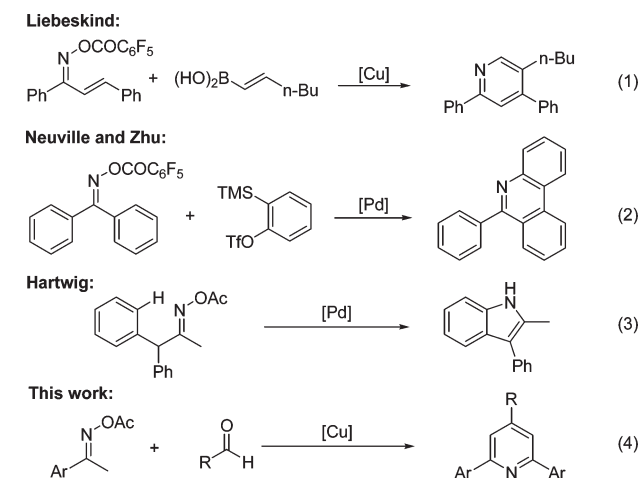
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and various kinds of functional materials.⁸ Although a variety of approaches toward substituted pyridines have been developed,⁹ versatile and efficient methods for the construction of pyridine rings which are compatible with various functional groups and using readily available starting materials remain highly desirable. Herein, we report a novel and efficient strategy for Cu-catalyzed coupling of oxime acetates with aldehydes for the synthesis of highly substituted pyridines (Scheme 1, eq 4).

Scheme 1. Transition Metal Catalyzed Coupling Reactions of Oxime Carboxylates

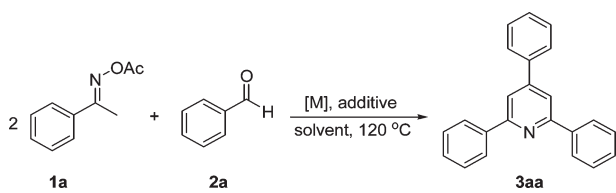


We began our study by investigating the coupling reaction of acetophenone oxime acetate **1a** with benzaldehyde **2a**. We were pleased to find that 2,4,6-triphenylpyridine **3aa** was formed in 30% yield accompanied by acetophenone as the only byproduct in the presence of a CuI catalyst in DMSO (Table 1, entry 1). The structure of the product **3aa** was unambiguously confirmed by X-ray diffraction analysis (see Supporting Information). This interesting result encouraged us to optimize the reaction conditions to give a general protocol for the synthesis of substituted pyridines. Therefore, different additives, copper catalysts, and solvents were screened for inhibition of the acetophenone formation (Table 1). To our delight, NaHSO₃ was discovered to efficiently inhibit the hydrolysis of oxime acetate,¹⁰ and the yield of 2,4,6-triphenylpyridine **3aa** was dramatically improved (Table 1, entry 2). Screening of copper catalysts, such as CuCl, CuBr, Cu₂O, and Cu(OAc)₂, revealed that CuBr was the most effective in the presence of NaHSO₃ (Table 1, entries 3–6). Other solvents such as NMP, 1,4-dioxane, and toluene are less effective (Table 1, entries 7–9). And low conversion was observed when Na₂SO₃ was employed as the additive (Table 1, entry 10).

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Table 1. Optimization of Conditions for Cu-Catalyzed Coupling of Oxime Acetate with Aldehyde^a



entry	catalyst	additive	solvent	yield (%)
1	CuI	—	DMSO	30
2	CuI	NaHSO ₃	DMSO	79
3	CuBr	NaHSO₃	DMSO	89
4	CuCl	NaHSO ₃	DMSO	77
5	Cu ₂ O	NaHSO ₃	DMSO	61
6	Cu(OAc) ₂	NaHSO ₃	DMSO	60
7	CuBr	NaHSO ₃	NMP	78
8	CuBr	NaHSO ₃	1,4-Dioxane	42
9	CuBr	NaHSO ₃	Toluene	35
10	CuBr	Na ₂ SO ₃	DMSO	32
11	—	NaHSO ₃	DMSO	0
12	Pd ₂ (dba) ₃	NaHSO ₃	DMSO	0

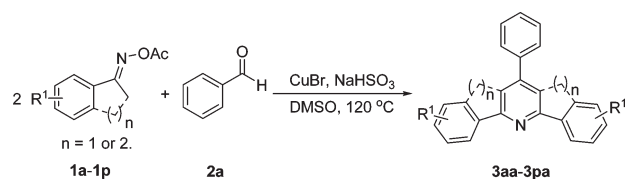
^a Reaction conditions: acetophenone oxime acetate **1a** (0.9 mmol), benzaldehyde **2a** (0.3 mmol), catalyst (10 mol %), and additive (0.9 mmol) in solvent (5 mL) under Ar at 120 °C for 2.5 h.

Furthermore, control experiments confirmed that no reaction occurred in the absence of a copper catalyst or in the presence of a Pd₂(dba)₃ catalyst (Table 1, entries 11–12). These results indicate that the Cu species did indeed act as the catalyst for cleavage of the N–O bond in oxime carboxylates in the reaction.

Under the optimized conditions for the Cu-catalyzed coupling of oxime acetates with aldehydes, the scope of this pyridine formation has been investigated. This transformation displayed high functional group tolerance and proved to be a quite general methodology. Oxime acetates with methyl, methoxyl, fluoro, chloro, and bromo groups on aryl rings all gave good to excellent yields of the corresponding pyridines (Table 2). Aryl chlorides and bromides were inert under the conditions suggesting that the Cu(I) catalyst preferentially reacts with the N–O bond of the oxime acetate over the C–X bonds (Table 2, entries 5–6). For the electronic effects of the transformation, the electron-rich oxime acetates showed better reactivity and gave slightly higher yields than electron-deficient ones (Table 2, entries 2–10). In addition, the 2-acetylnaphthalene oxime acetate **1k** and benzylideneacetone oxime acetate **1l** also underwent the desired reaction to give the corresponding pyridines **3ka** and **3la** in good yields respectively (Table 2, entries 11–12). An extensive investigation of the reaction shows that the fully substituted pyridines were achieved by using α-tetralone oxime acetates **1m–1n** or indanone oxime acetates **1o–1p** as substrates (Table 2, entries 13–16).

Various aldehydes were explored as well to extend the substrate scope, and the results are illustrated in

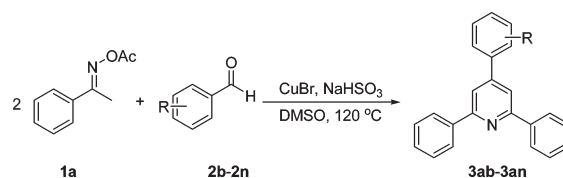
Table 2. CuBr-Catalyzed Coupling of Oxime Acetates with Benzaldehyde for Synthesis of Pyridines^a



entry	1	product	R ¹	yield (%)
1			H, 3aa	89
2			Me, 3ba	88
3			OMe, 3ca	90
4			F, 3da	80
5			Cl, 3ea	80
6			Br, 3fa	85
7			3ga	90
8			3ha	90
9			3ia	91
10			3ja	89
11			3ka	90
12			3la	78
13			H, 3ma	61
14			OMe, 3na	68
15			H, 3oa	63
16			Cl, 3pa	56

^a Reaction conditions: oxime acetate **1** (0.9 mmol), benzaldehyde **2a** (0.3 mmol), CuBr (10 mol %), and NaHSO₃ (0.9 mmol) in DMSO (5 mL) under Ar at 120 °C for 2.5 h.

Table 3. CuBr-Catalyzed Coupling of Acetophenone Oxime Acetate with Aldehydes for Synthesis of Pyridines^a



entry	2	product	R ¹	yield (%)
1			Me, 3ab	92
2			OMe, 3ac	76
3			NMe ₂ , 3ad	58
4			F, 3ae	95
5			Cl, 3af	91
6			Br, 3ag	88
7			NO ₂ , 3ah	45
8			3ai	95
9			OMe, 3aj	71
10			Cl, 3ak	70
11			3al	76
12			3am	86
13			3an	60

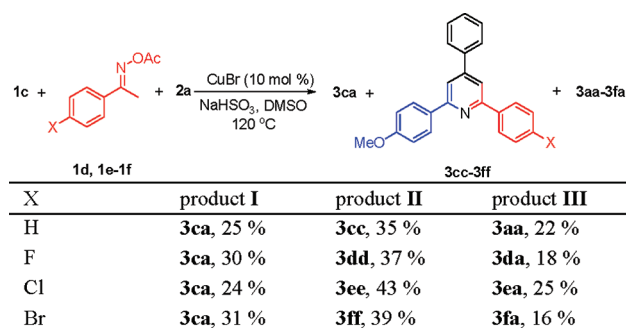
^a Reaction conditions: acetophenone oxime acetate **1a** (0.9 mmol), aldehyde **2** (0.3 mmol), CuBr (10 mol %), and NaHSO₃ (0.9 mmol) in DMSO (5 mL) under Ar at 120 °C for 2.5 h.

Table 3. Satisfactorily, the *para*-, *meta*-, and *ortho*-substituted aromatic aldehydes all gave the desired trisubstituted pyridines in good to excellent yields (Table 3, entries 1–11). *Ortho* MeO and Cl substituted benzaldehydes **2j–2k** proceeded smoothly to give the corresponding pyridines **3aj–3ak** in good yields implying that this transformation was insensitive to steric hindrance (Table 3, entries 9–10). In contrast with the substituted oxime acetates, electron-deficient aromatic aldehydes showed better reactivity and gave higher yields of pyridines than electron-rich ones (Table 3, entries 1–6). In addition, heteroaromatic aldehydes exhibit similar reactivity with benzaldehydes. Coupling

of 2-furaldehyde **2m** with acetophenone oxime acetate **1a** afforded 4-(furan-2-yl)-2,6-diphenylpyridine **3am** in 86% yield (Table 3, entry 12). It is noteworthy that 2,6-diphenylpyridine **3an** was also achieved in 60% yield when paraformaldehyde **2n** was employed (Table 3, entry 13).

For further extension of this methodology, the cross-coupling of two different oxime acetates with one aldehyde has been explored as well (Scheme 2). The three triarylpyridines were obtained in high total isolated yields (82–92%) in each of the reactions. The pyridines **3cc–3ff** were isolated as the major products (35–43%) suggesting that this protocol could be used for preparation of unsymmetrical pyridines directly.

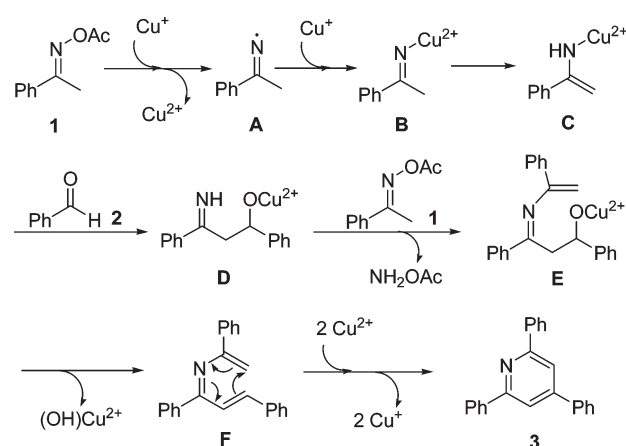
Scheme 2. Cross-Coupling of Two Different Oxime Acetates with Benzaldehyde^a



^aReaction conditions: oxime acetate **1c** (0.45 mmol), oxime acetate **1d**, or **1e–1f** (0.45 mmol), benzaldehyde **2a** (0.3 mmol), CuBr (10 mol %), and NaHSO₃ (0.9 mmol) in DMSO (5 mL) under Ar at 120 °C for 2.5 h.

The proposed mechanism of the present reaction is illustrated in Scheme 3. Cleavage of the N–O bond of the oxime acetate **1** by Cu⁺ gives the imine radical **A**, which is supposed to react rapidly with another Cu⁺ to give N–Cu²⁺ species **B**.^{11,12} Tautomerization of **B** affords the intermediate **C**, and nucleophilic addition of **C** to benzaldehyde forms imine intermediate **D**.¹² Then, condensation of imine intermediate **D** with a second oxime acetate **1** gives the intermediate **E**. Elimination of intermediate **E** produces an aza-hexa-1,3,5-triene intermediate **F**. Thermal electrocyclicization of intermediate **F** followed by rapid

Scheme 3. Proposed mechanism for Cu-Catalyzed Coupling of Oxime Acetates with Aldehydes



oxidation by Cu²⁺ affords the triarylpyridine **3**.^{5a} At the same time, the active Cu⁺ is regenerated. Alternatively, elimination of intermediate **D** could occur prior to the condensation.

In summary, we have developed a novel and efficient strategy for Cu-catalyzed coupling of oxime acetates with aldehydes for the synthesis of highly substituted pyridines. The N–O bond cleavage followed by multiple C–C and C–N bond formations was achieved by the copper catalyst under mild conditions. NaHSO₃ was discovered as a good inhibitor of hydrolysis of oxime acetates in this transformation. This novel method tolerates a wide range of functionality and allows for rapid elaboration of the readily available oxime acetates into a variety of symmetrical and unsymmetrical substituted pyridines in good to excellent yields. Current research is focused on extending the scope of the reaction.

Acknowledgment. This paper is dedicated to Professor Xumu Zhang on the occasion of his 50th birthday. We thank the National Natural Science Foundation of China (NSFC-21002077), Northwest University (PR09037, NF0913), and Education Department of Shaanxi Provincial Government (2010JK869) for financial support.

Supporting Information Available. Experimental procedures and spectral data for all products and X-ray data of **3aa** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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