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Conversion of Pyridine to Imidazo[1,2-*a*]pyridines by Copper-Catalyzed Aerobic Dehydrogenative Cyclization with Oxime Esters

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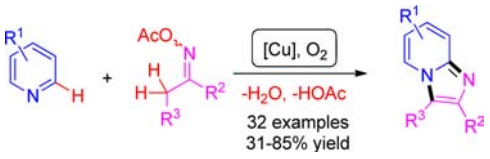
ABSTRACT



A rapid and environmentally friendly conversion of pyridine to imidazo[1,2-*a*]pyridines has been developed via copper-catalyzed aerobic dehydrogenative cyclization with ketone oxime esters.

Intensive attention has been paid to the transformation of pyridine and its derivatives, which provided convenient access to a broad range of functionalized N-containing organic molecules. However, in most cases, more reactive pyridinium salts were indispensable for the success of the transformation.[1] Direct functionalization of pyridine remains a significant challenge owing to the lower energy of the π-system relative to benzene.[2] In recent years, the transition-metal-catalyzed transformation of unactivated pyridine has triggered widespread interest due to the desirable synthetic flexibility and overall efficiency.[3,4]

On the other hand, the construction of pyridine-containing heteropolycycles from pyridine derivatives has been widely reported.[1,5] In particular, imidazo[1,2-*a*]pyridines, which represent an important class of natural products,

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pharmaceuticals, and bioactive compounds,[6] were intensively synthesized based on 2-aminopyridines[7,8] through condensation or/and oxidative coupling of the C−N bond. Instead of utilizing 2-aminopyridines, traditionally derived from pyridine, direct conversion of simple pyridine into the target heterocycles would be of great significance. However, there have been only a few examples designed toward imidazo[1,2-*a*]pyridines through direct conversion of pyridine. Recently, Fabio et al. reported a novel solvent- and catalyst-free reaction of pyridine-like heterocycles with 1,2-diaza-1,3-dienes, directly leading to imidazo[1,2-*a*]-pyridines, -quinolines, and -isoquinolines in good yields (Scheme 1a).[9] Despite the synthetic efficiency, this reaction suffers the limitation of inaccessible and substituent-restricted 1,2-diaza-1,3-dienes. During our preparation of this munascript, Fu et al. reported an efficient Cu-catalyzed aerobic cyclization of pyridine and *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amines for the synthesis of imidazo[1,2-*a*]pyridines with triazole as a leaving group (Scheme 1b).[10] As our continuing interest in *N*-heterocycle synthesis under a Cu/O_2 catalytic system,[11] herein, we describe a Cu-catalyzed aerobic cyclization of pyridine with easily accessible oxime esters for the preparation of imidazo[1,2-*a*]pyridine compounds (Scheme 1c). Compared with previous work, the present protocol features high efficiency and good functional group tolerance. Furthermore, the use of an environmentally friendly oxidant and the green byproducts generated make this transformation very practical and atom-economical.

We initially found that the imidazo[1,2-*a*]pyridine moiety can be formed with a promising 32% yield from pyridine (**1a**, 3.0 equiv) and acetophenone oxime acetate (**2a**, 1.0 equiv) with CuI (20 mol %) in *N*,*N*-dimethylformamide (DMF) under air at 95 °C for 2.0 h (Table 1, entry 1). Enhancement in yield was not observed upon screening other copper(I) catalysts such as CuBr (entry 2), CuCl (entry 3), and CuOTf (entry 4). Notably, Cu(II) catalysts such as $Cu(OTf)_2$ (entry 5) and $Cu(OAc)_2$ (entry 6) did not afford the imidazo-[1,2-*a*]pyridine product. Inorganic base additives, which would affect the interaction between Cu(I) and oxime esters,[12] proved to significantly influence this transformation. While NaOAc decreased the yield of **3aa**, $NaHSO_3$ and $NaHCO_3$ enhanced the yield to 49% and 45%, respectively. A marginal improvement was observed upon running the reaction with Na_2CO_3. To our delight, addition of Li_2CO_3 in this reaction

Scheme 1. Direct Transformation of Pyridine to Imidazo[1,2-*a*]pyridines

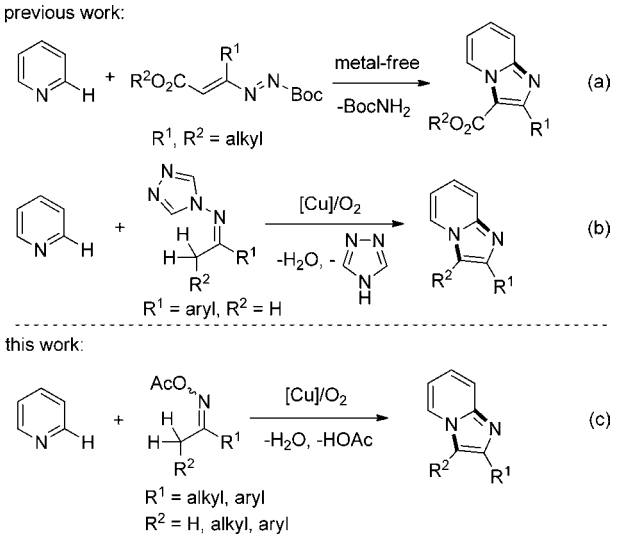
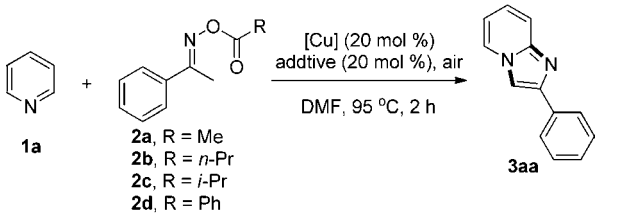


Table 1. Optimization of Reaction Conditions[a]



entry	oxime ester	cat. (20 mol %)	additive (20 mol %)	yield (%)[b]
1	**2a**	CuI	none	32
2	**2a**	CuBr	none	20
3	**2a**	CuCl	none	18
4	**2a**	CuOTf	none	9
5	**2a**	$Cu(OTf)_2$	none	trace
6	**2a**	$Cu(OAc)_2$	none	0
7	**2a**	CuI	NaOAc	25
8	**2a**	CuI	$NaHSO_3$	49
9	**2a**	CuI	$NaHCO_3$	45
10	**2a**	CuI	Na_2CO_3	33
11	**2a**	CuI	Li_2CO_3	89
12	**2a**	CuI	DABCO	trace
13[c]	**2a**	CuI	Li_2CO_3	88
14	**2b**	CuI	Li_2CO_3	15
15	**2c**	CuI	Li_2CO_3	62
16	**2d**	CuI	Li_2CO_3	40

[a] Unless otherwise indicated, the reaction was performed with oxime ester (0.3 mmol, 1.0 equiv), pyridine (0.9 mmol, 3.0 equiv), copper catalyst (0.06 mmol, 20 mol %), additive (0.06 mmol, 20 mol %) in DMF (1.0 mL) at 95 °C under air for 2.0 h. [b] Determined by GC analysis with tridecane as an internal standard. [c] Under an O_2 atmosphere.

(8) For synthesis of imidazo[1,2-*a*]pyridine from 2-aminopyridines based on oxidative coupling, see: (a) Yan, R.-L.; Yan, H.; Ma, C.; Ren, Z.-Y.; Gao, X.-A.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 2024. (b) Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 4386. (c) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073. (d) Wang, H. G.; Wang, Y.; Peng, C. L.; Zhang, J. C.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217. (e) Wang, H. G.; Wang, Y.; Liang, D. D.; Liu, L. Y.; Zhang, J. C.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (f) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (g) Bagdi, A. K.; Rahman, M.; Santra, S.; Majee, A.; Hajra, A. *Adv. Synth. Catal.* **2013**, *355*, 1741. (h) Mohan, D. C.; Donthiri, R. R.; Rao, S. N.; Adimurthy, S. *Adv. Synth. Catal.* **2013**, *355*, 2217. (i) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 2686.

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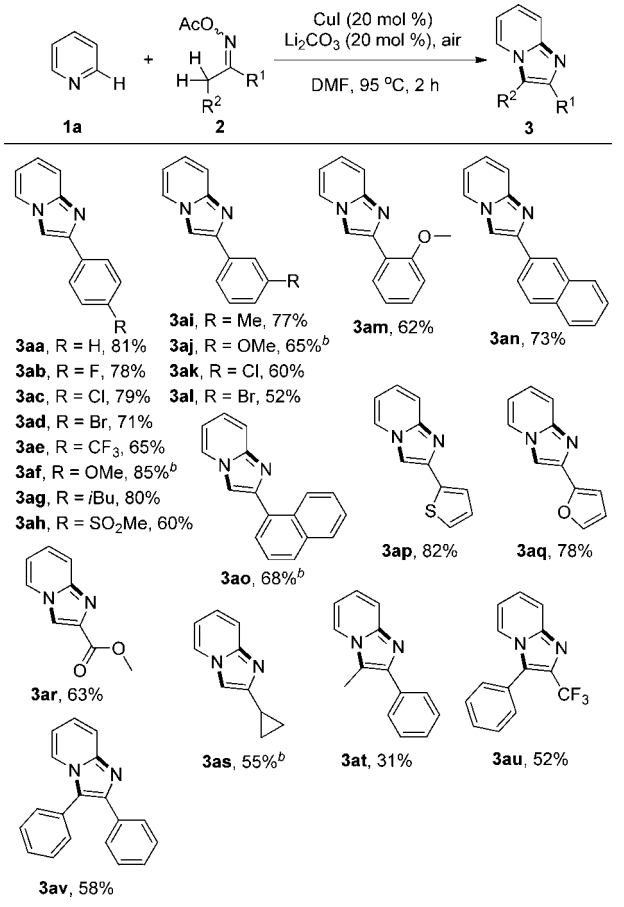
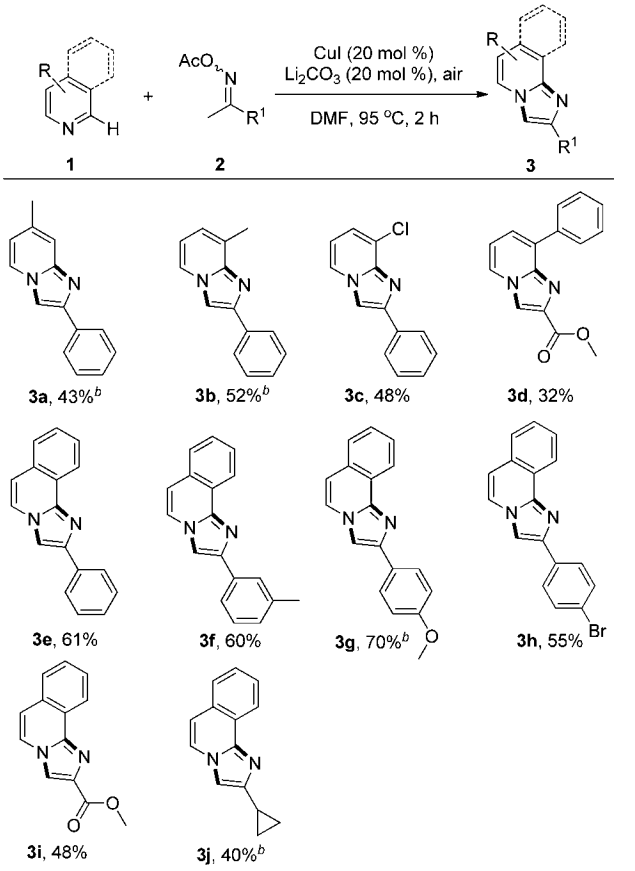
Scheme 2. Scope of Ketone Oxime Esters[a]



[a] Unless otherwise indicated, reaction conditions: see Table 1, entry 11. [b] Within 1.5 h.

Scheme 3. Scope of Pyridines and Isoquinoline[a]



[a] Unless otherwise indicated, reaction conditions: see Table 1, entry 11. [b] Within 1.5 h.

system gave a dramatic improvement, with the yield of **3aa** increasing up to 89% (entry 11). Unexpectedly an organic base such as DABCO completely prevented this transformation (entry 12). This reaction under an oxygen atmosphere led no obvious change in the yield (entry 13). Finally, other different acetophenone oxime esters (**2b**−**2d**) were tested under the catalytic system, and no further improvement in yield was observed (entries 14−16).

With the optimized reaction conditions in hand, we next set out to investigate the generality of the Cu-catalyzed cyclization with a variety of ketone oxime acetates (Scheme 2). A number of oximes derived from aryl methyl ketones smoothly participated in the reaction, affording the corresponding imidazo[1,2-*a*]pyridines **3aa**−**3am** in moderate to good yields, with tolerance of functional groups, including fluoro, chloro, bromo, trifluoromethyl, methoxyl, and methylsulfonyl groups. 1- or 2-naphthalenylethanone oximes afforded the products **3ao** and **3an**, respectively, in good yields. Oximes derived from thiophen-2-yl and furan-2-yl ketones were also productive, leading to the products (**3ap** and **3aq**) in 82% and 78% yield, respectively. Oximes derived from other aryl ketones such as propiophenone, 1,1,1-trifluoro-3-phenylpropan-2-one, and 2-phenylacetophenone afforded the products **3at**−**3av**, respectively, in moderate yields. Besides, oximes derived from methyl pyruvate and aliphatic ketone could efficiently afford imidazo[1,2-*a*]pyridines **3ar** and **3as**. Unfortunately, oximes derived from nonmethyl alkyl ketones such as pentan-3-one and cyclohexanone did not work. Among the oximes investigated, relatively electron-rich oximes, such as with methoxyl (**3af** and **3aj**), naphthalen-1-yl (**3ao**), and aliphatic (**3as**) groups, enabled the reaction time to be reduced to 1.5 h.

The substrate scope in substituted pyridines was also evaluated (Scheme 3). Generally, lower yields relative to pyridine were obtained with substituted pyridines. Interestingly, 3-substituted pyridines afforded products in moderate yield (**3b**−**3d**), with the C2-position of the pyridines participating rather than the C6-position. Unfortunately, C2-substituted pyridines did not prove fruitful when running the reaction with even more than 5 equiv of pyridines.

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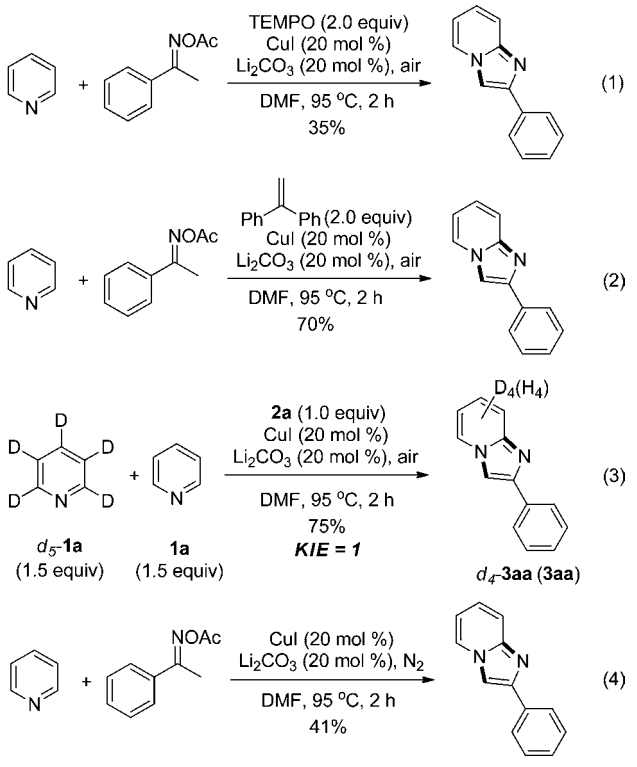
(13) Previous work on the transformation of 2-aminopyridines and methyl ketones (see ref 8g−8i) generally requires 24 h.

(14) See Supporting Information for details.

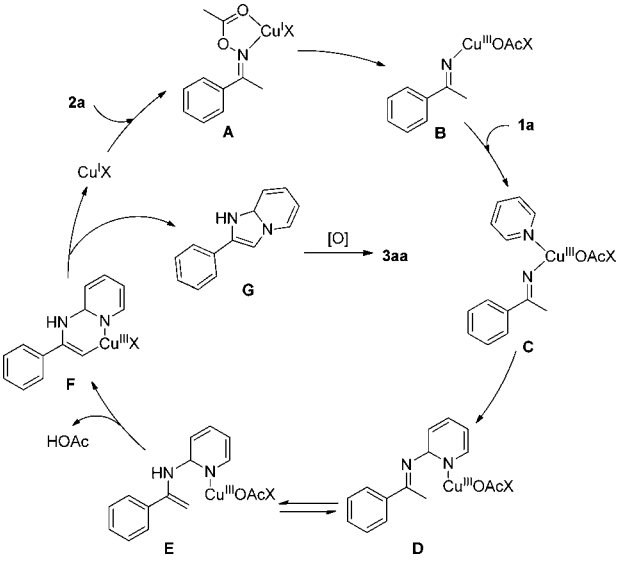
Pyridine-like heterocycles such as quinoline and isoquinoline were also subjected to these reaction conditions. While quinoline, just like a C2 substituted pyridine, could not work, isoquinoline was an effective substrate for this aerobic cyclization. When treated with various oximes derived from aryl methyl ketones, methyl pyruvate, and aliphatic ketone, isoquinoline reacted smoothly to afford moderate to good yields of substituted imidazo[2,1-*a*]-isoquinoline products (**3e**−**3j**), whereas oximes derived from nonmethyl ketones such as propiophenone and 2-phenylacetophenone featured very low activities (<15% yield). Compared with pyridine, other N-containing heteroaromatic compounds, such as pyrazine, pyrimidine, and 1,3,5-triazine, did not work in this aerobic cyclization.

To gain mechanistic insight into this reaction, some control experiments were conducted. Addition of a free radical scavenger TEMPO or ethene-1,1-diyldibenzene could not prohibit the cyclization (eqs 1 and 2), which indicated this reaction did not proceed through a radical mechanism. The intermolecular competition reaction was conducted using equal amounts of **1a** and D-labeled pyridine d_5-**1a**, corresponding to a KIE = 1 (eq 3), which was determined by ^{1}H NMR analysis of the isolated products. The measured KIE suggested that the H-abstraction from pyridine was not the rate-determining step during the oxidative cyclization. Additionally, ketone oxime esters could serve as an internal oxidant to promote this transformatiion because this reaction could afford a 41% yield of imidazo[1,2-*a*]pyridine **3aa** under a N_2 atmosphere (eq 4).



Based on the above experimental results and previous reports in terms of the Cu(I)-catalyzed transformation of oxime esters,[12] a possible mechanism is proposed as shown in Scheme 4. A Cu(III)-imino species **B** is formed via oxidative addition of Cu(I) to oxime esters. Then, insertion of pyridine into the Cu−N bond of **B** takes place at the 1,2-positions of the pyridine ring with a new Cu−N bond formation to afford intermediate **D**. Intramolecular H-abstraction of **E**, the tautomer of **D**, by Cu(III) results in a six-membered copper ring intermediate **F**. Finally, reductive elimination and oxidative aromatization lead to the final imidazo[1,2-*a*]pyridine product and regeneration of Cu(I). Additionally, pyridine aromatization of **D**, followed by oxidative cyclization, could also lead to the final product.[8g−i] However, the high efficiency of this reaction[13] (within 2 h) indicated it is more likely to proceed through direct reductive elimination of intermediate **F**. Moreover, intermediate **F** may provide the basis for the regioselectivity obtained with C3-subsituted pyridines.[14]

Scheme 4. Plausible Reaction Mechanism



In conclusion, we have developed a highly efficient Cu-catalytic system for the direct transformation of pyridine to imidazo[1,2-*a*]pyridine derivatives with ketone oxime esters. This protocol features advantages including high efficiency, an inexpensive catalyst (CuI), an economic and environmentally friendly oxidant (air), and green byproducts (HOAc and H_2O). Moreover, it might open up a new way to design complex molecules through direct conversion of unactivated pyridine.

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Supporting Information Available. Experimental procedure and characterization of compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.