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Copper-Catalyzed Aerobic Synthesis of 2-Arylpyridines from Acetophenones and 1,3-Diaminopropane

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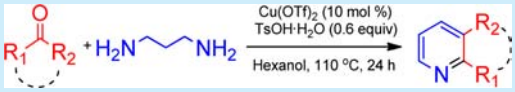
Supporting Information

ABSTRACT: A copper-catalyzed reaction providing direct access to 2-arylpyridines from acetophenones and 1,3-diaminopropane is described. A range of electronically diverse acetophenones undergo this transformation, affording 2-arylpyridines in good yields.

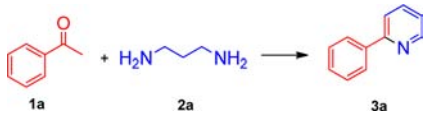


The pyridine-containing motif is present in many natural products, pharmaceutical agents, and functionalized materials.[1] Consequently, the development of methods for the synthesis of pyridine derivatives is important in medicinal chemistry and represents a worthwhile goal for organic synthesis. Traditional synthetic methods are based upon condensation reactions of carbonyl compounds. Recently, many new methods, including transition-metal-catalyzed cross-coupling, ring-closing metathesis, cycloadditions, radical reactions and microwave-assisted procedures, have also been developed.[2] In light of the importance of the pyridine moiety, developing an operationally simple approach for the preparation of pyridine derivatives from readily available starting materials remains in demand. Methyl ketones and their corresponding imines are attractive starting materials for the synthesis of azaheterocycles, not only because they are readily available and widely used chemical precursors but also because their C−H bonds can be directly functionalized to generate new C−C and C−N bonds in a step- and atom-economical fashion.[3]

Transition-metal-catalyzed oxidative cleavage of C(sp^3)−N bonds is of significant synthetic interest because such bonds are common in organic chemistry and are usually unreactive. Using amines as the carbon source for the generation of C−C bonds via the cleavage of C−N bonds has attracted considerable attention.[4] Primary alkyl amines represent the most simple and common amines. The cleavage of the C−N bond of a primary amine for the construction of azaheterocycles or drugs is especially desirable. Herein, for the first time, we report the copper-catalyzed C−N bond cleavage of a simple primary amine for the generation of 2-arylpyridines. The present protocol features advantages that include easily available starting materials, favorable atom economy, and the use of an environmentally friendly oxidant.[5]

Initially, we heated acetophenone **1a**, 1,3-diaminopropane **2a**, and $Cu(OTf)_2$ in ethanol at 80 °C for 72 h under an oxygen atmosphere (Table 1, entry 1). Fortunately, 2-phenylpyridine was isolated in 22% yield. Because we thought that an imine intermediate would be initially generated, we reasoned that an acid might promote this transformation. We therefore tested several acids as additives. All of the tested acids improved the yield of the product. *p*-Toluenesulfonic acid was the most effective additive for this reaction (Table 1, entry 6 vs entries 2−5). After screening other solvents and copper catalysts, we found that the use of other solvents and metal catalysts was ineffective (Table 1, entries 7−12 vs entry 6). The amounts of catalyst and additive were also optimized. The addition of 10 mol % of $Cu(OTf)_2$ and 0.6 equiv of *p*-toluenesulfonic acid was most effective (Table 1, entries 13−15). Nitrogen-containing ligands and other oxidants were also tested. Unfortunately, none of them was effective.[6] When hexanol was used as the

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (equiv)	solvent	acid	yield (%)[b]
1	$Cu(OTf)_2$ (0.6)	ethanol	none	22
2	$Cu(OTf)_2$ (0.6)	ethanol	MSA	43
3	$Cu(OTf)_2$ (0.6)	ethanol	acetic acid	48
4	$Cu(OTf)_2$ (0.6)	ethanol	TfOH	44
5	$Cu(OTf)_2$ (0.6)	ethanol	benzoic acid	51
6	$Cu(OTf)_2$ (0.6)	ethanol	$TsOH·H_2O$	60
7	$Cu(OTf)_2$ (0.6)	DCE	$TsOH·H_2O$	trace
8	$Cu(OTf)_2$ (0.6)	NMP	$TsOH·H_2O$	13
9	$Cu(OTf)_2$ (0.6)	CH_3CN	$TsOH·H_2O$	37
10	CuI (0.6)	ethanol	$TsOH·H_2O$	8
11	$Cu(OAc)_2$ (0.6)	ethanol	$TsOH·H_2O$	trace
12	$Cu(NO_3)_2$ (0.6)	ethanol	$TsOH·H_2O$	trace
13	$Cu(OTf)_2$ (0.1)	ethanol	$TsOH·H_2O$	60
14	$Cu(OTf)_2$ (0.02)	ethanol	$TsOH·H_2O$	20
15[c]	$Cu(OTf)_2$ (0.1)	ethanol	$TsOH·H_2O$	61
16[c,d,e]	$Cu(OTf)_2$ (0.1)	hexanol	$TsOH·H_2O$	64

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), solvent (0.5 mL), acid (0.8 equiv), O_2 (balloon), 72 h. [b]Isolated yields. [c]0.6 equiv of acid. [d]Temperature of 110 °C. [e]24 h.

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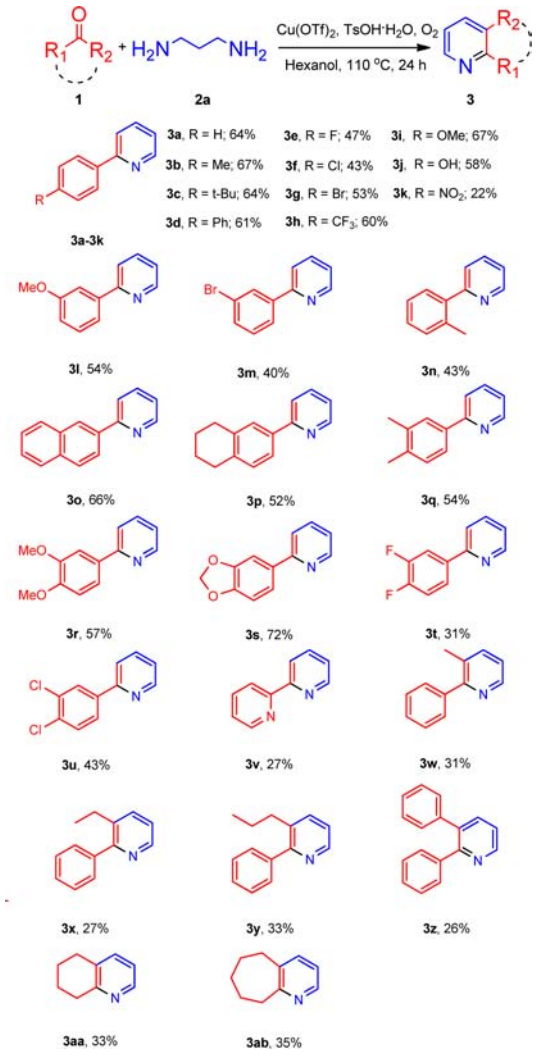
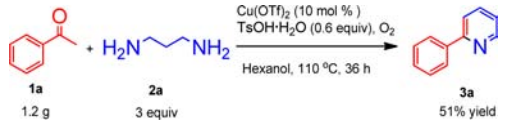
solvent, the reaction temperature could be increased to 110 °C, and the transformation was complete in 24 h, affording the product in 64% yield (Table 1, entry 16).

Having optimized the reaction conditions, we examined the scope of the reaction.[7] Acetophenones with an electron-donating or weak electron-withdrawing group on the *para*-position of the benzene ring afforded the desired products in good yields (Scheme 1, **3a**−**3j**). Strong electron-withdrawing groups showed an obvious negative effect on the yield (**3k**). The reaction tolerates a range of functionalities, including fluoro, chloro, bromo, trifluoromethyl, nitro, ether, and free phenol moieties. It should be noted that a phenol group often needs to be protected in an oxidative reaction. The product yield is also affected by the position of substituents on the aryl ring. Acetophenones bearing a *meta* or *ortho* substituent afforded the pyridines in lower yields than those with a *para* substituent (**3l** vs **3i**, **3m** vs **3g**, **3n** vs **3b**). 1-(Naphthalen-2-yl) ethanone also underwent this transformation, affording naphthylpyridine **3o** in 66% yield. Disubstituted acetophenones were then examined. Most gave the desired products in moderate yields (**3p**−**3u**). Interestingly, this reaction also occurred with aryl ketones with long-chain alkyl group and cyclic aliphatic ketones to afford 2,3-disubstituted pyridines (**3w**−**3z**, **3aa**, and **3ab**). In addition, this reaction was easily scaled up to the gram scale (Scheme 2).

Scheme 1. Scope of Ketones

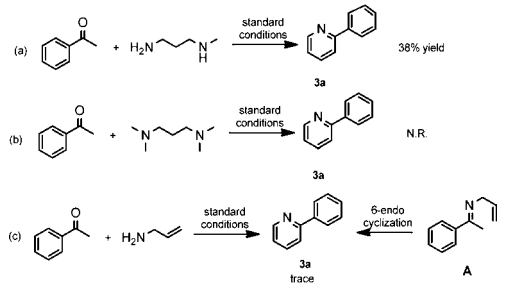


Scheme 2. Gram Scale Reaction



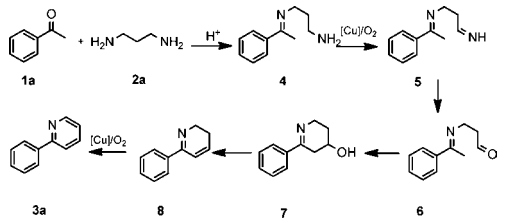
To elucidate the reaction mechanism, several control experiments were prepared (Scheme 3).

Scheme 3. Control Experiments



The reaction of *N*-methylpropanediamine with acetophenone under standard conditions afforded 2-phenylpyridine in 38% yield (Scheme 3, eq a). Tetramethylpropanediamine did not undergo this transformation. These results show that the formation of an imine intermediate is necessary for this transformation. Glorius et al.[8] reported that 2-phenylpyridine was generated as a side product, through 6-*endo* cyclization, in a Pd-catalyzed cyclization of imine **A** (eq c, right). However, only a trace amount of product **3a** was observed when allylamine was used in this reaction instead of propanediamine. Therefore, it seems impossible that this reaction proceeds through an allylamine intermediate. On the basis of these results and literature reports, a plausible mechanistic proposal is outlined in Scheme 4. The transformation begins with the condensation of the acetophenone with propanediamine. The resulting imine **4** is oxidized to diimine **5** by the Cu/O_2 system. Intermediate **5** undergoes hydrolysis, condensation, elimination, and oxidation to afford the product **3a**.

Scheme 4. Proposed Mechanism



In summary, we report a novel method for the synthesis of 2-arylpyridines from methyl ketones and 1,3-propanediamine through copper-catalyzed oxidative cyclization in an O_2 atmosphere. The reaction features cleavage of the C−N bond and formation of the C−C bond in one pot. Considering the readily available starting materials, the lack of an expensive metal catalyst, and the operationally straightforward proce-

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dures, the method is a valuable synthesis of the pyridine skeleton.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and spectroscopic data (^{1}H NMR and ^{13}C NMR) for the corresponding 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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■ REFERENCES

(1) (a) Zheng, S.; Zhong, Q.; Mottamal, M.; Zhang, Q.; Zhang, C.; LeMelle, E.; McFerrin, H.; Wang, G. *J. Med. Chem.* **2014**, *57*, 3369. (b) Bringmann, G.; Reichert, Y.; Kane, V. V. *Tetrahedron* **2004**, *60*, 3539. (c) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, 223. (d) Thomas, S. W.; Venkatesan, K.; Muller, P.; Swager, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 16641.

(2) (a) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 4945. (b) Liu, C.; Yang, W. *Chem. Commun.* **2009**, 6267. (c) Donohoe, T. J.; Bower, J. F.; Basutto, J. A.; Fishlock, L. P.; Procopiou, P. A.; Callens, C. K. A. *Tetrahedron* **2009**, *65*, 8969. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (e) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570. (f) Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schurmann, M.; Preut, H.; Jacob, T.; Arndt, H.-D. *J. Am. Chem. Soc.* **2008**, *130*, 13219.

(3) For selected recent examples, see: (a) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2012**, *14*, 6068. (b) Mohan, D. C.; Donthiri, R. R.; Rao, S. N.; Adimurthy, S. *Adv. Synth. Catal.* **2013**, *355*, 2217. (c) Zhang, Y.; Chen, Z.; Wu, W.; Zhang, Y.; Su, W. *J. Org. Chem.* **2013**, *78*, 12494. (d) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966. (e) Fei, Z.; Zhu, Y.-P.; Liu, M.-C.; Jia, F.-C.; Wu, A.-X. *Tetrahedron Lett.* **2013**, *54*, 1222. (f) Bagdi, A. K.; Rahman, M.; Santra, S.; Majee, A.; Hajra, A. *Adv. Synth. Catal.* **2013**, *355*, 1741. (g) Pilgrim, B. S.; Gatland, A. E.; McTernan, C. T.; Procopiou, P. A.; Donohoe, T. J. *Org. Lett.* **2013**, *15*, 6190. (h) Shi, Y.; Zhu, X.; Mao, H.; Hu, H.; Zhu, C.; Cheng, Y. *Chem.—Eur. J.* **2013**, *19*, 11553. (i) Huang, H.; Ji, X.; Wu, W.; Huang, L.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3774. (j) Ye, W.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756. (k) Chen, Z.-J.; Yan, Q.-Q.; Liu, Z.-X.; Xu, Y.-M.; Zhang, Y.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1. (l) Wu, Q.; Zhang, Y.; Cui, S. *Org. Lett.* **2014**, *16*, 1350. (m) Zhao, J.-W.; Huang, H.-W.; Wu, W.-Q.; Chen, H.-J.; Jiang, H.-F. *Org. Lett.* **2013**, *15*, 2604. (n) Giorgio, A.; Antonio, A.; Gabriele, B.; Sabrina, D. G.; Fabio, M.; Elisabetta, R. *J. Org. Chem.* **2003**, *68*, 6959.

(4) For selected examples, see: (a) Turner, N. J. *Chem. Rev.* **2011**, *111*, 4073. (b) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622. (c) Tang, R.-Y.; Guo, X.-K.; Xiang, J.-N.; Li, J.-H. *J. Org. Chem.* **2013**, *78*, 11163. (d) Chen, X.; Chen, T.; Zhou, Y.; Han, D.; Han, L.-B.; Yin, S.-F. *Org. Bio. Chem.* **2014**, *12*, 3802. (e) Wang, X.; Wang, Y.; Yuan, Y.; Xing, C.-H. *Tetrahedron* **2014**, *70*, 2195. (f) Hao, W.; Geng, W.; Zhang, W.-X.; Xi, Z. *Chem.—Eur. J.* **2014**, *20*, 2605. (g) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (h) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (i) Patil, R. D.; Adimurthy, S. *Adv. Synth. Catal.* **2011**, *353*, 1695. (j) Gao, L.; Tang, H.; Wang, Z. *Chem. Commun.* **2014**, *50*, 4085. (k) Ling, Z.; Yun, L.; Liu, L.; Wu, B.; Fu, X. *Chem. Commun.* **2013**, *49*, 4214.

(5) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(6) See the Supporting Information for additional data.

(7) Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), hexanol (0.5 mL), $TsOH·H_2O$ (0.6 equiv), O_2 (balloon), 110 °C, 24 h.

(8) Shi, Z.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *125*, 4992.