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COMMUNICATION

Copper-catalyzed intramolecular dehydro genative cyclization: direct access to sensitive formyl-substituted imidazo[1,2-*a*]pyridines

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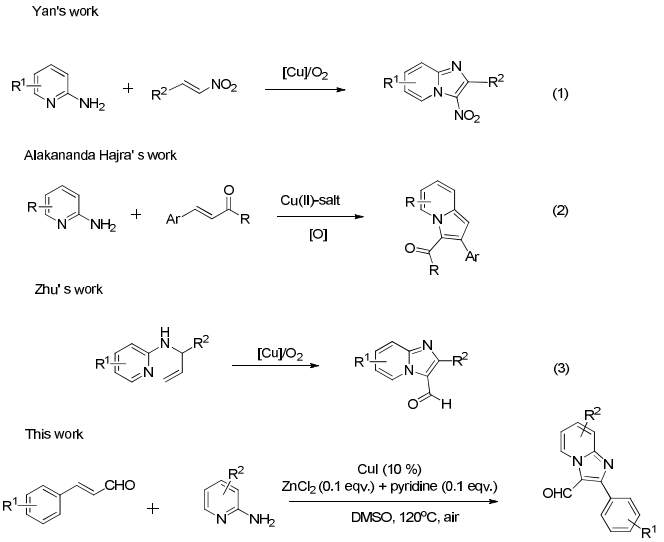
A direct method for the synthesis of formyl-substituted imidazo[1,2-*a*]pyridines was achieved easily from cyclization of aminopyridines and cinnamaldehydes via copper catalysis. This oxidative cyclization process involved direct C-H bond functionalization, C-C/C-N bonds formation. In this transformation, the sensitive aldehyde group was preserved under oxidant condition.

Substituted imidazo[1,2-*a*]pyridines, as attracting structural motifs, are found in natural products and organic chemistry with strong bioactivity profiles and interesting structural properties.[1] In particular, They are known to be crucial synthetic precursors to construct a wide range of biologically active compounds in medicinal chemistry,[2] and drug synthesis,[3] such as soraprazan, alpidem (a nonsedative anxiolytic),[4] andzolpidem (a hypnotic drug).[5] The exceptional promise of a broad therapeutic potential has drawn intense interest in developing concise approaches to synthesize substituted imidazo[1,2-*a*]pyridines. In the past several years, many well-documented modern methods had been developed for construction the scaffold of imidazo[1,2-*a*]pyridines.[6] However, there are very few general methods that convert commercially available or readily accessible materials to substituted imidazo[1,2-*a*]pyridines with aldehyde group. Thus, the synthesis of substituted imidazo[1,2-*a*]pyridines preserving the aldehyde group under oxidative conditions remains a challenging work.

Direct C-H functionalization and C-N bond formation represent as the powerful and ideal approaches for the synthesis of various heterocyclic compounds.[7] Especially, transition-metal catalyzed tandem reactions via direct C-H functionalization and C-N bond formation as an active field of organic chemistry have been evolved as powerful tools to generate of heterocyclic compounds.[8] Moreover, air as an ideal oxidant has drawn much attentions in for its abundance, environment-friendly and attractive industrial prospects.[9] Recently, Yan's [10] and Hajra's [11]group and our group had reported the direct method to synthesize substituted imidazopyridines (Scheme 1, eq.1-2). In 2011, Zhu and co-workers elegantly developed a direct methology to formyl-substituted imidazo[1,2-*a*]pyridines via copper-catalyzed intramolecular dehydrogenative aminooxygenation in satisfactory to high yields (Scheme 1, eq.3).[12] Inspired by their works and some our previously studies about the synthesis of heterocyclic compounds,[13] herein, we report a facial and direct method to synthesize formyl-substituted from aminopyridines and cinnamaldehydes via copper catalyst.



Scheme 1. Strategies for the syntheses of imidazopyridines

We first investigated the reaction of cinnamaldehyde (**1a**) and pyridin-2-amine (**2a**) in DMF at 100 °C with Cu-

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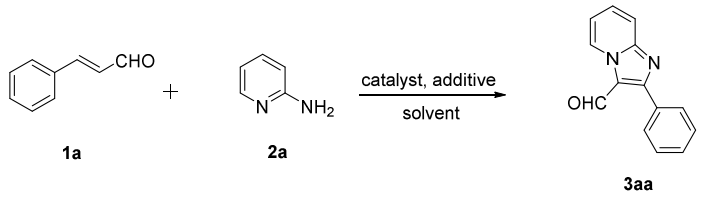
Table 1. Optimization of reaction condition [a]



1a 2a 3aa

entry	catalyst	additive	solvent	temp	yield
1	CuI		DMF	100	55
2	CuBr		DMF	100	21
3	CuCl		DMF	100	20
4	$Cu(OAc)_2$		DMF	100	26
5	$Cu(OTf)_2$		DMF	100	19
6	CuI		DMF	120	60
7	CuI	CF_3COOH (0.2)	DMF	120	68
8	CuI	TSOH (0.2)	DMF	120	43
9	CuI	PivOH (0.2)	DMF	120	70
9	CuI	PivOH (0.2)	DMSO	120	72
10	CuI	PivOH (0.2)	PhMe	reflux	-
11	CuI	PivOH (0.2)	CH_3CN	reflux	32
12	CuI	$ZnCl_2$(0.1)	DMSO	120	70
13	CuI	$ZnCl_2$(0.1)+1,10-phenanthroline (0.1)	DMSO	120	74
14	CuI	$ZnCl_2$(0.1)+TMEDA (0.1)	DMSO	120	63
15	CuI	$ZnCl_2$(0.1)+ Pyridine (0.1)	DMSO	120	80
16[c]	CuI	$ZnCl_2$(0.1)+ Pyridine (0.1)	DMSO	120	62
17		$ZnCl_2$(0.1)+Pyridine (0.1)	DMSO	120	-

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), additive, solvent (2 mL), 8h. [b] Yields of isolated products. [c] The reaction was carried out under air. [c] Under O_2.

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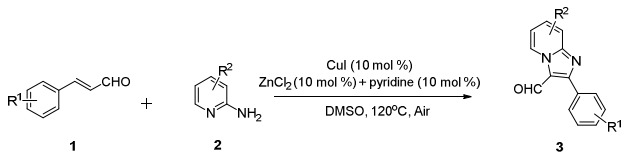
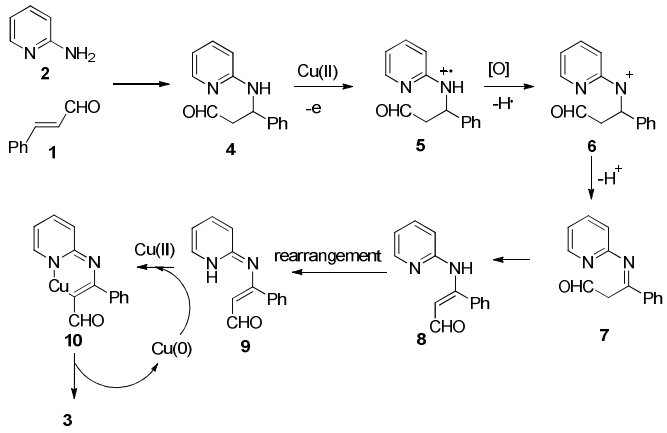
Table 2. Synthesis of substituted formyl-substituted imidazo[1,2-*a*]pyridines from aminopyridines and cinnamaldehydes [a]



entry		R^1		R^2	product	yields
1	1a	H	2a	H	3aa	80
2	1a	H	2b	3-Me	3ab	32
3	1a	H	2c	5-Me	3ac	42
4	1a	H	2d	6-Me	3ad	trace
5	1a	H	2e	3-OCH_2Ph	3ae	38
6	1a	H	2f	4-Cl	3af	52
7	1a	H	2g	5-Cl	3ag	88
8	1a	H	2h	5-Br	3ah	79
9	1a	H	2i	5-F	3ai	95
10	1a	H	2j	4-COOEt	3aj	78
11	1a	H	2k	5-Br,6-Me	3ak	52
12	1b	2-Me	2a	H	3ba	66
13	1c	3-Me	2a	H	3ca	44
14	1d	4-Cl	2a	H	3da	36
15	1e	4-Br	2a	H	3ea	32
16	1f	2-NO_2	2a	H	3fa	38
17	1b	2-Me	2g	5-Cl	3bg	trace
18	1g		2a	H	3ga	-

catalysis. To our delight, an expected product of 2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde (**3aa**) was isolated in 55% yield (Table 1, entry 1). Surprisingly, the aldehyde of cinnamaldehyde was preserved under the oxidative conditions. Substituted imidazo[1,2-a]pyridines with free intact formyl group can be easily converted to various functional groups and show enormous potential applications in organic synthesis.[7] Encouraged by this interesting result, we screened copper catalysts to increase the yield of this transformation and CuI showed the highest activity for this reaction (Table 1, entry 2-5). Increasing temperature of reaction just slightly improved the yield (Table 1, entry 6). Then, the influencing parameters of additives, oxidants and solvents was evaluated, the use of $ZnCl_2$ and pyridine as additive led to a significant improvement and offered the target compound in 80% yield (Table 1, entry 15). Obviously, $ZnCl_2$ promotes the reaction by coordinating with the oxygen of aldehyde. Nevertheless, without copper salts as catalyst, no desired product was obtained (Table 1, entry 17).

With the optimized reaction conditions in hand, we extended the substrate scope of this reaction, and the results are illustrated in Table 2. Various aminopyridines with methyl, methoxyl, cyano, fluoro, chloro, bromo, ester and benzyloxyl groups proceeded smoothly and generated the corresponding compounds successfully in moderate to good yields. As shown in Table 2, the results indicated that this transformation was sensitive to electronic effect of aminopyridines. The aminopyridines with the electron-drawing groups show better reactivity and gave the desired products in higher yields. Whereas, the electron-donating groups on aminopyridines significantly affected the efficiency of the process and resulted in lower yields (Table 2, entry 2-10). Further studies showed that a variety of substituted cinnamaldehydes successfully produced the desired products **3** with lower yields. Similarly, the electronic effect of cinnamaldehydes also affected this transformation obviously. The electron-rich cinnamaldehydes show better reactivity and gave higher yields than electron-deficient ones (Table 2, entry 12-16). Unfortunately, substituted pyrrole **3bg** was not achieved well by using **1b** and **2g** as substrate (Table 2, entry 17). Moreover, when (*E*)-but-2-enal **1g** and **2a** were subjected to the standard condition, no desired product was detected.



Scheme 2. Proposed mechanism

Based on the experimental results, we propose the reaction mechanism shown in Scheme 2. Firstly, cinnamaldehyde **1** and pyridin-2-amine **2** undergo Michal addition to form the intermediate **4**. Then, the radical cation **5**, which is generated by one electron oxidation, produces the nitrenium ion **6** by hydrogen abstraction with oxidation. Then imine **7** is formed by proton elimination from **6** and equilibrates to enamine **8**. Subsequently, enamine **8** would rearrange to the complex **9.** and complex **9** coordinates with the copper (II) catalyst to form the intermediate **10**,[14,15] Finally, the target molecular **3aa** is afforded by reductive elimination of copper catalyst.

In conclusion, we have developed a Cu-catalyzed oxidative cyclization method with aminopyridines and cinnamaldehydes to form formyl-substituted imidazo[1,2-*a*]pyridines. In this transformation, the sensitive aldehyde group was preserved under oxidant conditions. This approach, in which the air was used as oxidant, provided a simple and practice method to synthesis the substituted formyl imidazo[1,2-*a*]pyridines.

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Notes and references

1 (a) K. C. Rupert, J. R. Henry, J. H. Dodd, S. A. Wadsworth, D. E. Cavender, G. C. Olini, B. S. Fahmy, *J. Bioorg. Med. Chem. Lett.,* 2003, **13**, 347; (b) A. R. Katritzky, Y.-J. Xu, H. Tu, *J. Org. Chem.,* 2003, **68**, 4935; (c) Y. Katsura, S. Nishino, Y. Inoue, M. Tomoi, H. Takasugi, *Chem. Pharm. Bull*., 1992, **40**, 371; (d) S. M. Hanson, E. V. Morlock, K. A. Satyshur, C. Czajkowski, *J. Med. Chem.,* 2008, **51**, 7243; (e) M. H. Wiegand, *Drugs* 2008, **68**, 2411.

2 (a) Y. Katsura, S. Nishino, Y. Inoue, M. Tomoi, H. Takasugi*, Chem. Pharm. Bull.,* 1992, **40**, 371; (b) Y. Rival, G. Grassy, G. Michel, *Chem. Pharm. Bull.,* 1992, **40**, 1170; (c) K. C. Rupert, J. R. Henry, J. H. Dodd, S. A. Wadsworth, D. E. Cavender, G. C. Olini, B. Fahmy, J. J. Siekierka, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 347; (d) S. M. Hanson, E. V. Morlock, K. A. Satyshur, C. Czajkowski, *J. Med. Chem.,* 2008, **51**, 7243.

3 (a) G. C. Moraski, L. D. Markley, P. A. Hipskind, H. Boshoff, S. Cho, S. G. Franzblau, M. J. Miller, *ACS Med. Chem. Lett.,* 2011, **2**, 466; (b) M. H. Wiegand, *Drugs* 2008, **68**, 2411.

4 S. Z. Langer, S. Arbilla, J. Benavides, B. Scatton, *Adv. Biochem. Psychopharmacol.,* 1990, **46**, 61.

5 T. S. Harrison, G. M. Keating, *CNS Drugs* 2005, **19**, 65.

6 (a) A. J. Stasyuk, M. Banasiewicz, M. K. Cyranski, D. T. Gryko, *J. Org. Chem.,*2012, **77**, 5552; (b) M. Adib, E. Sheikhi, N. Rezaei, *Tetrahedron Lett*.,2011, **52**, 3191; (c) E. F. DiMauro, J. M. Kennedy, *J. Org. Chem.,* 2007, **72**, 1013; (d) K. Groebke, L. Weber, F. Mehlin, *Synlett* 1998, *661*; (e) S. K. Guchhait, A. L. Chandgude, G. Priyadarshani, *J. Org. Chem*., 2012, **77**, 4438; (f) P. Liu, L.-S. Fang, X. Lei, G.-Q. Lin, *Tetrahedron Lett*., 2010, **51**, 4605; (g) N. Chernyak, V. Gevorgyan, *Angew. Chem*., 2010, **122**, 2803; *Angew. Chem. Int. Ed.,* 2010, **49**, 2743; (h) Z.-J. Cai, S.-Y. Wang, S.-J. Ji, *Adv. Synth. Catal.,* 2013, **355**, 2686; (i) C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han, A. Lei, *Chem. Commun.,* 2012, **48**, 11073; (j) H. Wang, Y. Wang, C. Peng, J. Zhang, Q. Zhu, *J. Am. Chem. Soc.,* 2010, **132**, 13217; (k) K. S. Masters, T. R. M. Rauws, A. K. Yasav, W. A. Herrebout, B. V. Veken, B. U. W. Mases, *Chem. Eur. J.,* 2011, **17**, 6315; (l) I. R. Lahoz, C. Sicre, A. Navarro-Vazquez, C. S. Lopez, M. M. Cid, *Org. Lett.,* 2009, **11**, 4802; (m) L. Ma, X. Wang, W. Yu, B. Han, *Chem. Commun.,* 2011, **47**, 11333; (n) D. C. Mohan, R. R. Donthiri, S. N. Rao, S. Adimurthy, *Adv. Synth. Catal.,* 2013, **355**, 2217; (o) X. Wang, L. Ma, W. Yu, *Synthesis* 2011, **15**, 2445; (p) S. Santra, A. K. Bagdi, A. Majee, A. Hajra, *Adv. Synth. Catal.,* 2013, **355**, 1065; (q) A. K. Bagdi, M. Rahman, S. Santra, A. Majee, A. Hajra, *Adv. Synth. Catal.,* 2013, **355**, 1741.

7 (a) S. R. Dubbaka, P. Vogel, *Angew. Chem. Int. Ed.,* 2005, **44**, *7674*; (b) J. Q. Yu, Z. J. Shi, *C-H Activation:* Springer, Berlin, 2010; (c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.,* 2010, **110**, 624; (d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev*., 2007, **107**, 174; (e) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.,* 2008, **41**, 222; (f) H. Li, Y. Li, X.-S. Zhang, K. Chen, X. Wang, Z.-J. Shi, *J. Am. Chem. Soc.,* 2011, **133**, 15244; (g) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.,* 2011, **111**, 1293; (h) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.,* 2010, **110**, 624; (i) C. Coperet, *Chem. Rev.,* 2010, **110**, 656; (j) T. W. Lyons, M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147; (k) I. A. Mkhalid, I. J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.,* 2010, **110**, 890; (l) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.,* 2012, **45**, 788. (m) W. Wang, X. Peng, X. Qin, X. Zhao, C. Ma, C-H. Tung, Z. Xu, *J. Org. Chem.,* 2015, **80**, 2835. (n) X. Peng, W. Wang, C. Jiang, D. Sun, Z. Xu, C-H. Tung, *Org. Lett.,* 2014, **16**, 5354.

8 (a) C.-H. Jun, *Chem. Soc. Rev.,*2004, **33**, 610; (b) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed*., 2011, **50**, 11062; (c) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.,* 2011, **111**, 1780; (d) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.,* 2012, **45**, 851; (e) J. Yu, H. Yang, Y. Jiang, H. Fu, *Chem. Eur. J.,* 2013, **19**, 4271.

9 (a) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem., Int. Ed*., 2011, **50**, 11062; (b) Z. Shi, Y. Cui, N. Jiao, *Org. Lett.,* 2010, **12**, 2908.

10 (a) R.-L. Yan, J. Luo, C. -X. Wang, C. -W. Ma, G. -S. Huang, Y. -M. Liang, *J. Org. Chem*., 2010, *75*, 5395; (b) H. Yan, R. Yan, S. Yang, X. Gao, Y. Wang, G. Hang, Y. Liang, *Chem. Asian. J*., 2012, **7**, 2028.

11 (a) K. Monir, A. K. Bagdi, S. Mishra, A. Majee, A. Hajra, *Adv. Synth. Catal.,* 2014, **356**, 1105; (b) R.-L. Yan, H. Yan, C. Ma, Z.-Y. Ren, X.-A. Gao, G.-S. Huang, Y.-M. Liang, *J. Org. Chem.,* 2012, **77**, 2024.

12 H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang, Q. Zhu, *Angew. Chem*., 2011, *123*, 5796; *Angew. Chem. Int. Ed*., 2011, **50**, 5678.

13 L.-H. Zhai, L.-H. G, Y.-H. Luo, Y. Yang, B.-W. Sun, *Org. Process Res. Dev*. 2015, **19**, 849.

14 (a) G. Zhang, J. Miao, Y. Zhao, H. Ge, *Angew. Chem.,* 2012, **124**, 8443; *Angew. Chem. Int. Ed.,* 2012, **51**, 8318; (b) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.,* 2012, **134**, 9098; (c) Z. Shi, M. Suri, F. Glorius, *Angew. Chem.,* 2013, **124**, 2992; *Angew. Chem. Int. Ed.,*2013, **52**, 4892.

15 S. Ueda, H. Nagasawa, *J. Am. Chem. Soc.,* 2009, **131**, 15080.

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