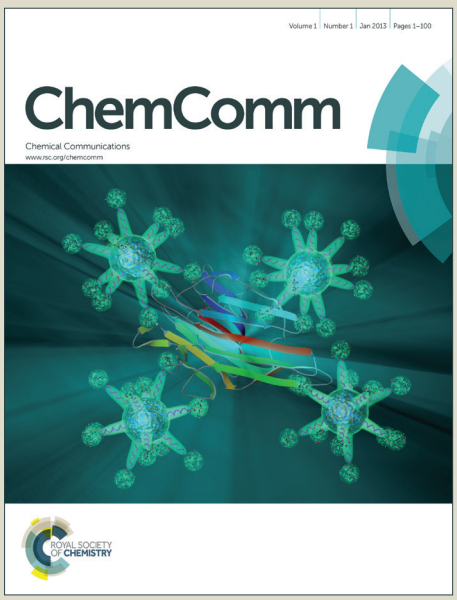
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

A novel and one-pot method for the synthesis of substituted furopyridines: I_2-mediated oxidative reaction of enaminones via tandem cyclization under metal-free conditions

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

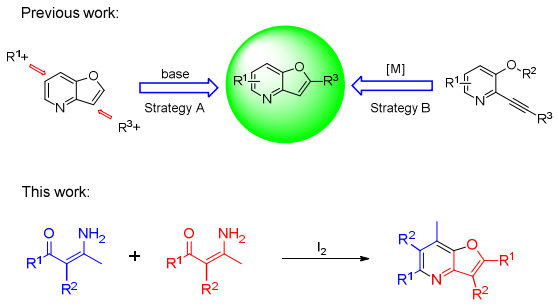
www.rsc.org/

Rulong Yan*, Xiaoni Li, Xiaodong, Yang, Xing Kang, Likui Xiang, Guosheng Huang*

A novel and I_2-mediated oxidative tandem cyclization reaction of simple enaminones has been developed for the synthesis of substituted furopyridines through C-C/C-N/C-O bonds formation in one pot procedure. In this reaction, substituted furopyridines are obtained in moderate to good yields. Moreover, I/Br-substituted furopyridines are achieved successfully via electrophilic substitution reaction of NIS/NBS.

The tandem reactions have received considerable interests for its simplifying reaction steps, reducing waste, and maximizing atom economy, and have been developed as powerful and eco-friendly strategies for synthesis of complex molecules from simple starting materials.[1] With the development of C-H bond activation, oxidative tandem reactions have emerged as attractive and challenging methods to construct heterocyclic compounds.[2] With the increased concern on environmental issues, the metal-free oxidative tandem reactions have presented as highly-efficient protocol, and also have opened doors for numerous possibilities for developing new methods of synthesizing heterocyclic compounds from simple substrates in line with the green chemistry idea.[3]

The furopyridine nucleuses have been found as key structural units in a variety of therapeutic areas.[4] For example, this structural units have been used as candidates of HIV protease inhibitors.[5] Therefore, intense efforts have been focused on the development of new synthesizing methods. Two general strategies for the synthesis of furopyridines have been followed: formal insertion of new functional groups to the scaffold of furopyridines (Scheme 1 strategy A)[6] and transition-metal catalyzed tandem reaction cyclization of pyridinyl allyl ethers (Scheme 1 strategy B).[7] Both processes suffer from several disadvantages, such as the involvement of expensive metal compounds, complex substrates, or harsh reaction conditions. To our best knowledge, there is no method which directly leads to the scaffold of furopyridines from simple substrates by one-step reaction. Inspired by recent studies in synthesizing heterocyclic compounds with simple starting materials,[8] we made an unexpected finding: substituted furopyridines can be formed by I_2-mediated reaction of enaminone amides in one-pot with C-C/C-N/C-O bonds formation.



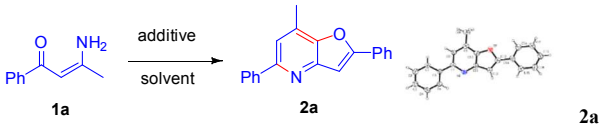
Scheme 1. The methods of synthesizing substituted furopyridines

In our initial experiments, (*Z*)-3-amino-1-phenylbut-2-en-1-one (**1a**) was chosen as test substrate for this cyclization using I_2 in DMSO under air at 100 °C to achieve the transformation. To our delight, an unexpected product 7-methyl-2,5-diphenylfuro [3,2-*b*] pyridine (**2a**) was obtained in 36% yield, and we confirmed the structure of **2a** unambiguously through an X-ray crystal analysis. Then other solvents such as DMF, MeCN, and toluene were evaluated, MeCN was found as the best solvent for

Dr. R. Yan, X. Li, X. Kang, X. Liu, L. Xiang, X. Zhou, Prof. Dr. G. Huang State Key Laboratory of Applied Organic Chemistry, Key laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou,730000 (China)
Fax: 0931-8912596 E-mail: yanrl@lzu.edu.cn, hgs@lzu.edu.cn

Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic, analytical and X-Ray data. CCDC 1012693, 1012635. See DOI: 10.1039/c000000x/

Table 1. Optimization of reaction condition [a]



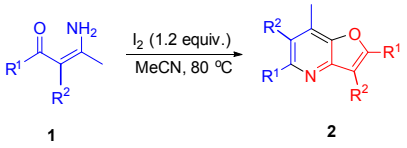
entry	Additive/equiv	solvent	temp	yield[b]
1	I_2 (1.2)	DMSO	100	36
2	I_2 (1.2)	DMF	100	38
3	**I_2 (1.2)**	**MeCN**	**80**	**87**
4	I_2 (1.2)	toluene	100	12
5	NIS (1.2)	MeCN	80	18
6	PIDA (1.2)	MeCN	80	-
7	TBAI (1.2)	MeCN	80	-
8	I_2(0.1)	MeCN	80	10
9	I_2(0.5)	MeCN	80	46
10[c]	I_2(1.2)	MeCN	80	86
11	I_2(1.2)	MeCN	60	63

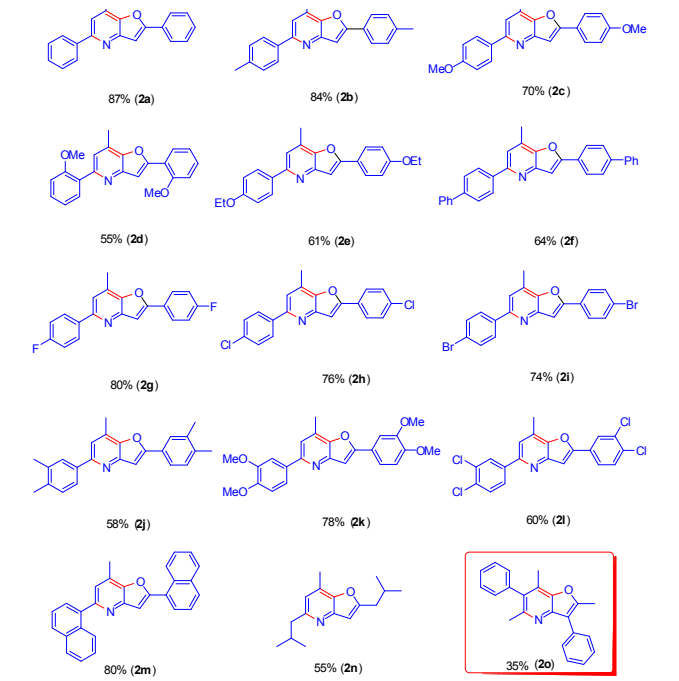
[a] Reaction conditions: **1a** (0.3 mmol), additive, solvent (2 mL). [b] Yields of isolated products. [c] The reaction was carried out under O_2 (1 atm). Entry in bold highlights optimized reaction conditions, and the reaction time was monitored by TLC. DMSO = Dimethyl sulfoxide, DMF= *N*,*N*-Dimethylformamide.

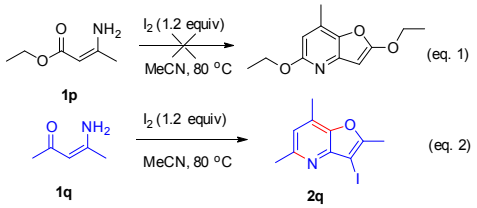
the reaction (Table 1, entries 1–6). Furthermore, when the I_2 was changed to *N*-iodosuccinimide (NIS), iodosobenzene diacetate (PIDA), and tetrabutylammonium iodide (TBAI), I_2 showed the highest activity for this reaction and resulted in 87% yield. After screening on temperature, the highest yield of **2a** was achieved when the reaction was carried out at 80 °C in MeCN with I_2 (Table 1, entry 3).

With the optimized reaction conditions in hand, we explored the substrate scope of this reaction, and the results are illustrated in Scheme 2. Generally, the transformation displayed well functional group tolerance, and was proved to be an efficient methodology for preparation of substituted furopyridines. enaminones with methyl, methoxyl, fluoro, chloro, and phenyl groups on aryl rings all gave the desired furopyridines in moderate to good yields. Obviously, the nature of the substituent on the aromatic rings did not significantly affect the yields of the products (**2b**-**2l**). As shown in Scheme 2, the naphthyl-substituted enaminone was also tolerated in this transformation and produced 7-methyl-2,5-di(naphthalen-2-yl)furo[3,2-*b*]pyridine **2m** in 80% yield. Moreover, this transformation can be also performed even on the enaminone with alkyl groups, and the desired products **2n** was obtained in 55% yield. It was worth mentioning that when more challenging substrate of (*Z*)-4-amino-3-phenylpent-3-en-2-one **1o** was employed for this transformation, the desired product 2,5,7-trimethyl-3,6-diphenylfuro[3,2-*b*]pyridine **2o** was isolated in 35% yield. Further investigation indicated that ethyl (*Z*)-3-aminobut-2-enoate **1p** was subjected to the standard condition, no desired

Scheme 2. I_2-involved oxidative tandem cyclization of enaminones for synthesis of substituted furopyridines





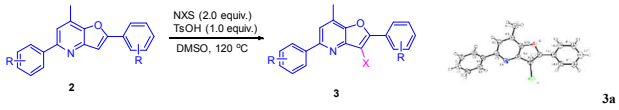


Scheme 3. The reaction of **1p** and **1q**

product was detected (Scheme 3. eq. 1). This result was caused by the weaker electrophilicity of ester carbonyl in **1p**. Interestingly, when **1q** was performed under optimized condition, the desired substituted furopyridine was not observed. Instead, an unprecedented product **2q** was isolated in 21% yield (Scheme 3. eq. 2). This result of I-substituted furanpyridine, which mean that steric hindrance of methyl group was less than other groups in substituted furopyridines, inspired us to optimize the reaction conditions to provide a general protocol for the synthesis of halide furopyridines.

Encouraged by the above results, the substituted furopyridine

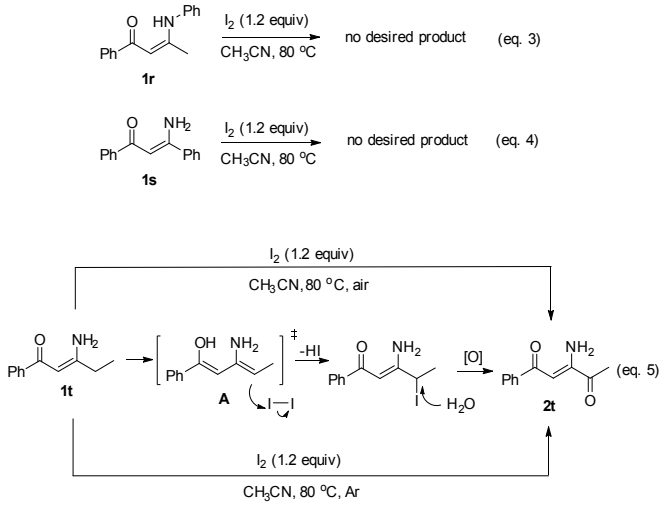
Table 2. The reaction of substituted furopyridines and NXS [a]



entry	R	X	product	yield
1	H	I	**3a**	68
2	Me	I	**3b**	67
3	OMe	I	**3c**	45
4	3,4-diMe	I	**3d**	60
5	F	I	**3e**	70
6	Br	I	**3f**	80
7	naphthyl	I	**3g**	25
8	H	Br	**3h**	45
9	F	Br	**3i**	43

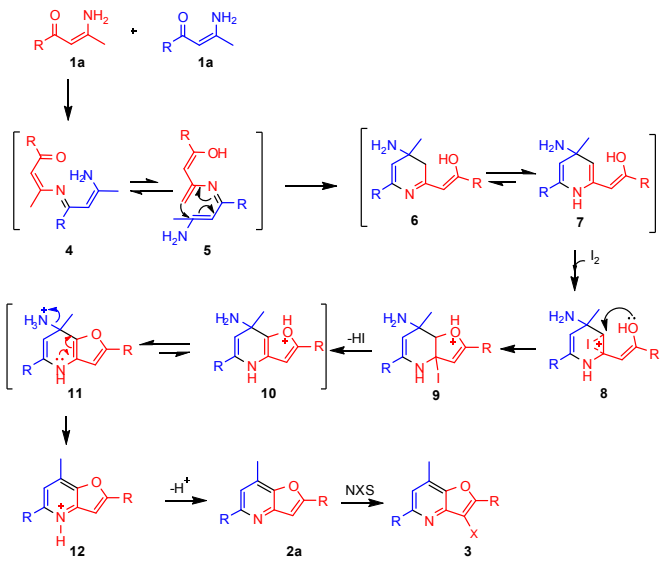
[a] Reaction conditions: **2a** (0.3 mmol), NXS (0.6 mmol), acid (0.3 mmol), solvent (2 mL), 120 °C. [b] Yields of isolated products.

2a was chose as model substrate to optimize the reaction condition. After screening on I_2, NIS, acids and other different parameters, the highest yield of **3a**, which was confirmed unambiguously through an X-ray crystal analysis, was achieved when the reaction was carried out with NIS (2.0 equiv.), *p*-toluene sulfonic acid (TsOH) (1.0 equiv.) in DMSO at 120 °C (see supporting information).Then, we investigated the substrate scope of this electrophilic substitution reaction (Table 2). Diverse substrates underwent this substituted reaction with NIS to afford the corresponding products in moderate to excellent yields. Similarly, the substituents on the aromatic rings did not affect the yields of the product. Moreover, the substrates with Br and F groups proceeded well under optimized conditions and gave the corresponding products in good yields. To our delight, even the substituted furopyridines were employed to react with *N*-bromosuccinimide (NBS) under optimized reaction conditions, the desired products were also isolated in moderate yields (Table2, entries 8-9).



Scheme 4. Control experiments

To probe the mechanism further, some control experiments were investigated. When (*Z*)-1-phenyl-3-(phenylamino)but-2-en-1-one (**1r**) and (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one (**1s**) was carried out under standard conditions, no desired products was obtained (Scheme 4, eq. 3-4). In order to have insight to the 1-phenylpent-2-en-1-one (**1t**) was subjected to the optimized mechanism of this transformation, The substrate of (*Z*)-3-amino-conditions, unexpected product (*Z*)-3-amino-1-phenylpent-2-ene-1,4-dione (**2t**) was produced in 52% yield. Even this reaction was performed under argon protected, similarly, the product **2t** also was detected and separated in 47% yield. This result means that the substrate **1t** would equilibrate to generate the intermediate **A**, which is attacked by H_2O, Then, the **2t** is formed via oxidation in this transformation (Scheme 4, eq.5). So the compound **A** would be the intermediate of the transformation.



Scheme 5. Proposed mechanism

On the basis of the results described above, a plausible mechanism is proposed in Scheme 5. The reaction starts form the combination of two molecular substrate **1** to generate imine **4**, which equilibrates to intermediate **5** under the reaction condition. Subsequently, intramolecular cyclization of **4** leads to intermediate **6**. In this transformation, the **6** would transfer to **7** via rearrangement under optimized conditions. The iodonium ion **8**, which is generated by iodination of **7**, produces intermediate **9** via intramolecular attacks of the hydroxyl and the furan unit **10** is formed by elimination of the HI. Then, **11** is followed by protonation of the primary amine and elimination to give **12** via aromatization. And the furopyridine **2** is afforded by deprotonation of **12**. Finally, the product **3** is achieved via electrophilic substitution reaction.

In conclusion, we have developed a simple, novel and efficient I_2-mediated strategy to synthesize substituted furopyridines via oxidative tandem cyclization of simple enaminones. This transformation constructs the skeleton of furopyridines through C-C/C-N/C-O bonds formation in one-pot manner. Moreover, I/Br-substituted furopyridines were afforded efficiently via electrophilic substitution reaction of NIS/NBS.

This work was supported by National Natural Science Foundation of China (21202067) and the Fundamental Research Funds for the Central Universities (lzujbky-2014-71).

Notes and references

1 (a) L.-N. Guo, X.-H. Duan and Y.-M. Liang, *Acc. Chem. Res*., 2011, **44**, 111; (b) Z.-X. Jia, Y.-C. Luo and Xu, P.-F. *Org. Lett*., 2011, **13**, 832; (c) B. EftekhariSis, M. Zirak and A. Akbari, *Chem. Rev*., 2013, **113**, 2958; (d) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev*., 2013, **113**, 3084; (e) A. Padwa, *Chem. Soc. Rev*., 2009, **38**, 3072. (f) Z.-J. Zhang, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Org. Lett.,* 2013, **15**, 4822.

2 (a) H. Pellissier, *Chem. Rev.* 2013, **113**, 442; (b) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res*., 2011, **44**, 1156; (c) M. M. Hussain and P. J. Walsh, *Acc. Chem. Res*., 2008, **41**, 883; (d) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev*., 2005, **105**, 1001; (e) T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev*., 2009, **38**, 3010.

3 (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624; (b) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev*., 2011, **111**, 1293; (c) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q.Yu, *Acc. Chem. Res*., 2012, **45**, 788. (d) X. Li, Y. Du, Z. Liang, X. Li, Y. Pan, K. Zhao, *Org. Lett.,* 2009, **11**, 2643. (e) Liu, X.; Cheng, R.; Zhao, F.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.,* 2012, **14**, 5480. (f) Sun, X.; Lyu, Y.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.,* 2013, **15**, 6222. (g) Rapoport, H.; Van Sickle, A. P. *J. Org. Chem.,* 1990, **55**, 895. (h) Hoffman, J. M., Jr. U.S. Patent 4,808,595, 1989; *Chem. Abstr.,* 1989, **111**, 115159m.

4 (a) D. G. Wishka, D. R. Graber, E. P. Seest, L. A. Dolak, F. Han, W. Watt and J. Morris, *J. Org. Chem*., 1998, **63**, 7851; (b) D. G. Wishka, D. R. Graber, L. A. Kopta, R. A. Olmsted, J. M. Friis, J. D. Hosley, W. J. Adams, E. P. Seest, T. M. Castle, L. A. Dolak, B. A. Keiser, Y. Yagi, A. Jeganathan, S. T. Schlachter, M. J. Murphy, G. J. Cleek, R. A. Nugent, S. M. Poppe, S. M. Swaney, F. Han, W. Watt, W. L. White, T.-J. Poel, R. C. Thomas, R. L. Voorman, K. J. Stefansky, R. G. Stehle, W. G. Tarpley and J. Morris, *J. Med. Chem*., 1998, **41**, 1357; (c) W. B. Choi, I. N. Houpis, H. R. O. Churchill, A. Molina, J. E. Lynch, R. P. Volante, P. G. Reider and A. O. King, *Tetrahedron Lett*., 1995, **36**, 4571; (d) I. N. Houpis, W. B. Choi, P. J. Reider, A. Molina, H. Churchill, J. Lynch and R. P. Volante, *Tetrahedron Lett*., 1994, **35**, 355; (e) J. Uenishi, T. Takagi, T. Ueno, T. Hiraoka, O. Yonemitsu and H. Tsukube, *Synlett*, 1999, **1**, 41.

5 (a) P. Gros, Y. Fort and P. J. Caubere, Chem. Soc., *Perkin Trans. 1* 1997, 3071; (b) P. Gros andY. Fort, *Eur. J. Org. Chem*., 2002, 3375; (c) P. C. Gros, and Y. Fort, *Eur. J. Org. Chem*., 2009, 4199; (d) M. Schlosser and F. Mongin, *Chem. Soc. Rev*., 2007, **36**, 1161; (e) A. Carrr, P. Rousselle, J. - C. Florent and E. Bertounesquea, *Adv. Synth. Catal*., 2012, **354**, 2751; (f) A. Chartoire, C. Comoy and Y. Fort, *Tetrahedron*, 2008, **64**, 10867; (g) A. Chartoire, C. Comoy and Y. Fort, *J. Org. Chem*., 2010, **75**, 2227. (h) Carrer, A.; Rousselle, P.; Florent, J.-C.; Bertounesque, E. *Adv. Synth. Catal.,* 2012, **354**, 2751.

6 (a) I. Husain, M. Saquib, V. Bajpai, B. Kumar and A. K. Shaw, *J. Org. Chem*., 2011, **76**, 8930; (b) A. Arcadi, S. Cacchi, S. D. Giuseppe, G. Fabrizi and F. Marinelli, *Org. Lett.* 2002, **4**, 2409; (c) P. Cironi, J. Tulla-Puche, G. Barany, F. Albericio and M. AÄ lvarez, *Org. Lett*., 2004, **6**, 1405; (d) D. Yue, T. Yao and R. C. Larock, *J. Org. Chem*., 2005, **70**, 10292; (e) A. P. VanSickle and H. Rapoport, *J. Org. Chem*., 1990, **55**, 897; (f) T. Lechel, J. Dash, I. Brüdgam and H.-U.Reißig, *Eur. J. Org. Chem*., 2008, 3647.

8 (a) R.-L. Yan, J. Huang, J. Luo, P. Wen, G.-S. Huang and Y.-M. Liang, *Synlett*, 2010, **7**, 1071; (b) R.-L. Yan, J. Luo, C.-X. Wang, C.-W. Ma, G.-S. Huang and Y.-M. Liang, *J. Org. Chem*., 2010, **75**, 5395; (c) R.- L. Yan, H. Yan, C. Ma, Z.-Y. Ren, X.-A. Gao, G.-S. Huang and Y.-M. Liang, *J. Org. Chem*., 2012, **77**, 2024; (d) H. Yan, R. Yan, S. Yang, X. Gao, Y. Wang, G. Huang and Y. Liang, *Chem. Asian J*., 2012, **7**, 2028; (e) R. Yan, X. Liu, C. Pan, X. Zhou, X. Li, X. Kang and G. Huang, *Org. Lett*., 2013, **15**, 4876. (f) R. Yan, X. Kang, X. Zhou, X. Li, X. Liu, L. Xiang, Y. Li, G. Huang, *J. Org. Chem.*, 2014, **79**, 465.

