RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

RSCPublishing

COMMUNICATION

I_2-catalyzed oxidative cyclization synthesis indolizines from aromatic/aliphatic olefins and α-picoline derivatives

Cite this: DOI: 10.1039/xoxxoooooox

Likui Xiang, Fuming Zhang, Baohua Chen, Xiaobo Pang, Xiaodong Yang, Guosheng Huang, Rulong Yan*

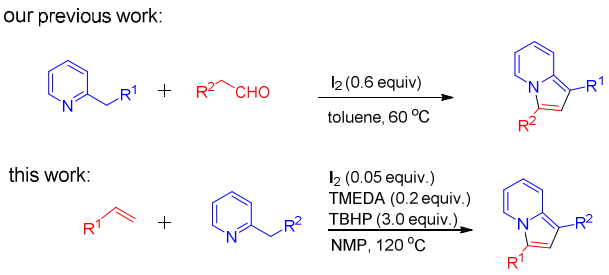
Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

A novel and I_2-catalyzed intermolecular oxidative tandem cyclization reaction of aromatic/aliphatic olefins and α-picoline derivatives has been achieved for the synthesis of indolizines under metal-free conditions. In this transformation, substituted indolizines are obtained in moderate to good yields through C-C/C-N bonds formation in one pot.

Synthesis of indolizines have attracted considerable interest due to their diverse and enhanced biological activities in organic synthesis. The skeleton of indolizines is an important key structures in many pharmacological compounds[1] and materials science.[2] As a result, great development has been achieved to the synthesis of indolizines in past years. Between them, some elegant procedures have been accomplished by cyclization starting from pyridinium *N*-methylides and specific C2 functionalization of pyridines.[3] With the development of C-H bond activation, the metal-catalyzed direct functionalization of indolizines was explored recently.[4] From economic points of view, the oxidative tandem reaction has emerged as a powerful and versatile synthetic tool for construction of indolizines through C-C/C-N bonds formation. More recently, Lei group have reported a reagent-free oxidative cyclization approach for synthesis of indolizines derivatives with α-picoline derivatives and nitroolefins.[5] And our group also have reported a direct I_2-mediated oxidative cyclization method to synthesize indolizines from aromatic/aliphatic enolizable aldehydes and 2-pyridyl acetates/acetone/acetonitrile.[6] However, it is still a great challenge to synthesize indolizines with readily accessible substrate through metal-free oxidative tandem cyclization.



Scheme 1. The methods of synthesizing substituted indolizines

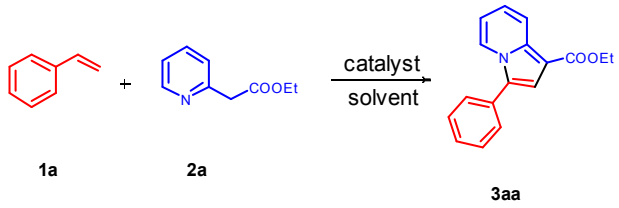
To overcome some of the disadvantages associate with metal catalysts and complex substrates, I_2/TBHP reaction system is appropriate candidates for both academic and industrial communities to our transformation.[7] Iodine and olefins, as common and easily available substrates, have been widely used in constructing the scaffolds of heterocyclic compounds.[8] On the basis of our previous studies in synthesis heterocyclic compounds,[9] we envisaged that substituted indolizines could be realized from olefins and *α*-picoline derivatives via I_2-catalyzed. With this in mind, our initial investigation began by treating styrene (**1a**) and ethyl 2-(pyridin-2-yl)acetate (**2a**) with I_2 (10 mol %) and *t*-butyl hydroperoxide (TBHP) (3 equiv.) in DMF at 120 °C. Gratifyingly, the desired product ethyl 3-phenylindolizine-1-carboxylate (**3aa**) was isolated in 54% yield (Table 1, entry 1). Herein, we reported a direct I_2-catalyzed oxidative cyclization protocol for the synthesis of substituted indolizines with alkyl pyridines and aldehydes according to the interesting results.

In order to improve the yield of **3aa**, different solvents were screened initially and NMP was found as the best one for this reaction (Table 1, entry 3). After changing the amount of I_2, the

L. Xiang, F. Zhang, B. Chen, X. Pang, X. Yang, Prof. G. Huang, Dr. R. Yan
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

Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data. See DOI: 10.1039/c000000x/

Table 1. Optimization of reaction condition [a]



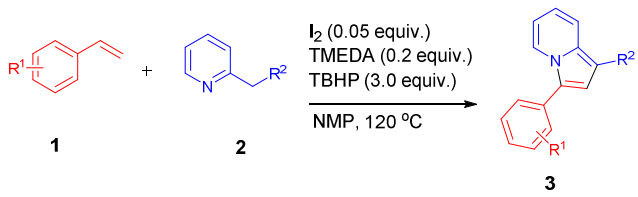
entry	catalyst	additive	oxidant	solvent	yield [b]
1	I_2 (0.1)		TBHP	DMF	54
2	I_2 (0.1)		TBHP	DMSO	36
3	I_2 (0.1)		TBHP	NMP	62
4	I_2 (0.1)		TBHP	THF	60
5	I_2 (0.1)		TBHP	MeCN	58
6	I_2 (0.6)		TBHP	NMP	-
7	I_2 (0.05)		TBHP	NMP	67
8	I_2 (0.05)		DTBP	NMP	trace
9	I_2 (0.05)		benzoyl peroxide	NMP	-
10	I_2 (0.05)		O_2	NMP	trace
11	I_2 (0.05)	pyridine	TBHP	NMP	69
12	I_2 (0.05)	Et_3N	TBHP	NMP	70
13	I_2 (0.05)	TMEDA	TBHP	NMP	74
14	I_2 (0.05)	1,10-phe nanthrolin	TBHP	NMP	71
15	I_2 (0.05)	PPh_3	TBHP	NMP	60
16	I_2 (1.0)			NMP	-
17	-		TBHP	NMP	-
18	-	TMEDA	TBHP	NMP	-

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), additive (0.2 equiv.), oxidant (3.0 equiv.) in 2 mL of solvent for 4h. [b] Isolated yield. DMF = Dimethyl formamide, DMSO = Dimethyl sulfoxide, THF = Tetrahydrofuran, NMP = *N*-methyl-2-pyrrolidone.

higher yield was achieved when 0.05 equiv. I_2 was used in this transformation. Then various oxidants were also evaluated for this reaction, TBHP showed the highest activity for this reaction (Table 1, entry 7). Further studies showed that the use of *N*,*N*-ligands could promote the reaction, and the yield of **3aa** was increased to 78% when 20 mol % TMEDA was employed as additive (Table 1, entry 13). Moreover, I_2 played an important role in this reaction because no desired product was generated without I_2 (Table 1, entries 17-18).

With the optimized conditions in hand, the scope of the substituted styrenes and 2-pyridyl acetates/acetone/acetonitrile were examined and the results are illustrated in Table 2. It was gratifying to find that a variety of substituted styrenes could react with 2-pyridyl acetates/acetonitrile smoothly and furnished the desired products in moderate yields. As shown in Table 2, the

Table 2. Synthesis of substituted indolizines from substituted styrenes and 2-pyridyl acetates/acetone/acetonitrile [a]

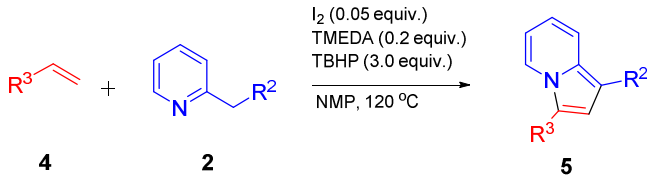


entry		1		2	product	yields [b]
		R^1		R^2		
1	**1a**	H	**2a**	COOEt	**3aa**	74
2	**1b**	2-Me	**2a**	COOEt	**3ba**	71
2	**1c**	3-Me	**2a**	COOEt	**3ca**	66
4	**1d**	4-Me	**2a**	COOEt	**3da**	59
5	**1e**	4-*t*Bu	**2a**	COOEt	**3ea**	61
6	**1f**	2,5-diMe	**2a**	COOEt	**3fa**	72
7	**1g**	2,4,6-triMe	**2a**	COOEt	**3ga**	54
8	**1h**	4-OMe	**2a**	COOEt	**3ha**	70
9	**1i**	4-CH_2Cl	**2a**	COOEt	**3ia**	41
10	**1j**	4-Ph	**2a**	COOEt	**3ja**	61
11	**1k**	2-F	**2a**	COOEt	**3ka**	81
12	**1l**	4-F	**2a**	COOEt	**3la**	62
13	**1m**	2-Cl	**2a**	COOEt	**3ma**	71
14	**1n**	3-Cl	**2a**	COOEt	**3na**	84
15	**1o**	4-Cl	**2a**	COOEt	**3oa**	63
16	**1p**	2-Br	**2a**	COOEt	**3pa**	78
17	**1q**	4-Br	**2a**	COOEt	**3qa**	52
18	**1a**	H	**2b**	COOMe	**3ab**	70
19	**1h**	4-OMe	**2b**	COOMe	**3hb**	62
21	**1m**	2-Cl	**2b**	COOMe	**3mb**	72
22	**1n**	3-Cl	**2b**	COOMe	**3nb**	73
23	**1a**	H	**2c**	CN	**3ac**	35
24	**1a**	H	**2d**	COMe	**3ad**	trace

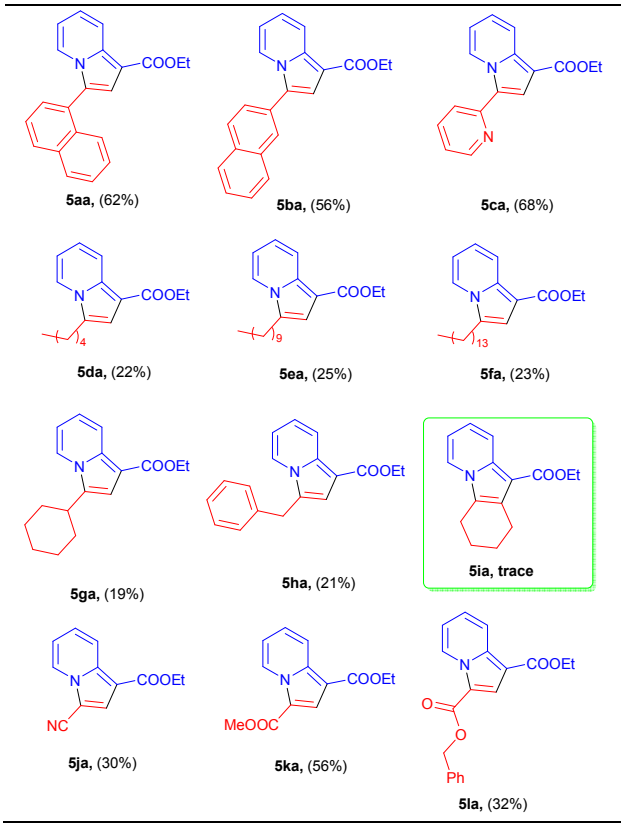
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), I_2 (0.05 equiv), TMEDA (0.2 equiv.), TBHP (3.0 equiv.) in 2 mL NMP for 4h. [b] Isolated yield.

substituents on the aryl ring of the styrenes did not have a certain influence on the formation of products. Specially, the styrenes bearing an electron withdrawing groups, such as F, Cl, Br, generated the desired products in slightly higher yields than the electron-donating ones. Moreover, the substrate **2a** was changed to **2b** and **2c**, the process underwent efficient cyclization and the desired products were afforded in moderate yields. When 2-pyridylacetone was employed for this reaction, only trace amount of the desired products was detected.

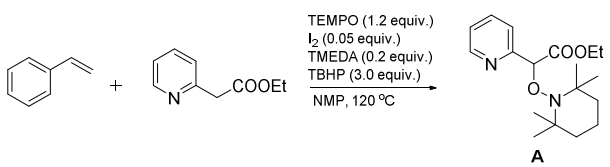
Table 3. Synthesis of substituted indolizines from substituted aliphatic alkenes and 2-pyridyl acetates



4 2 5

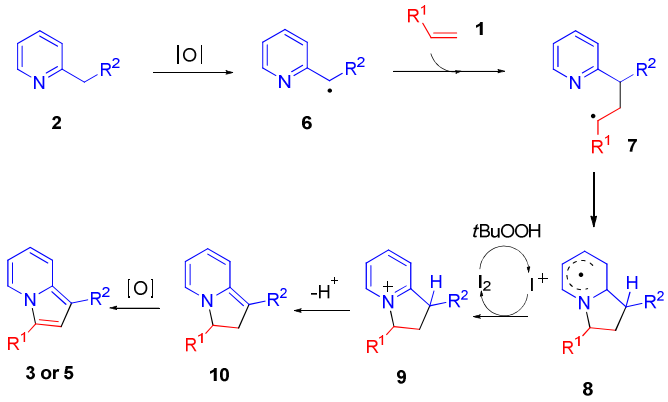


To further extent the substrate scope, we then pay more attention on some more challenging alkenes to evaluate the procedure. Gratifyingly, the alkenes with different functional groups displayed efficient compatibility and produced the target products in moderate yields. The vinylnaphthalene (**4a** and **4b**) and 2-vinylpyridine (**4c**) performed well and gave the products in this process. Specially, the aliphatic alkenes could react under optimized conditions and form the desired products except cyclohexene. Interestingly, even aliphatic alkenes, bearing cyano and ester groups, were also well tolerated in this transformation and offered the target products in moderate yields.



Scheme 2. Control experiment

In order to gain insights into the mechanism further, control experiment was investigated. The radical trapping experiment was performed in the presence of 2,2,6,6-teramethylpiperidine oxide (TEMPO). Indeed, the addition of 1.2 equivalent. of TEMPO that led to the oxidative process was remarkably suppressed and a useful intermediate **A** was isolated (Scheme 2). The intermediate **A** gave a powerful evidence for the mechanism of the reaction.



Scheme 3. Proposed mechanism

Base on the above experiments, a proposed mechanism is shown in Scheme 3. Initially, the substrate **2** generates a radical intermediate **6** under optimized conditions. Then, **6** adds to the substrate **1** to afford radical **7** which can be further cyclized to carbocation **8** via intramolecular radical addition. Subsequently, **8** undergoes oxidation to form intermediate **9** in the presence of I_2 and TBHP, which can further undergo proton elimination to give **10**. Eventually, the product **3** or **5** would be afforded by the oxidation of intermediate **10**.

In summary, we have developed a novel approach to synthesis substituted indolizines catalyzed by I_2. Substituted aromatic/aliphatic olefins and α-picoline derivatives all can be tolerated well in this transformation and generate the desired products in moderate yields.

This work was supported by National Natural Science Foundation of China (21202067, 21372102) and the Fundamental Research Funds for the Central Universities (lzujbky-2014-71).

Notes and references

1 (a) R. C. Oslund, N. Cermak and M. H. Gelb, *J. Med. Chem.,* 2008, **51**, 4708; (b) A. Hazra, S. Mondal, A. Maity, S. Naskar, P. Saha, R. Paira, K. B. Sahu, P. Paira, S. Ghosh, C. Sinha, A. Samanta, S. Banerjee and N. B. Mondal, *Eur. J. Med. Chem.,* 2011, 2132.

2 (a) J. B. Henry, R. J. MacDonald, H. S. Gibbad, H. McNab, A. R. Mount, *Phys. Chem. Chem. Phys.,* 2011, **13**, 5235; (b) B. Liu, Z. Wang, N. Wu, M. Li, J. You, J. Lan, *Chem. -Eur. J.,* 2012, **18**, 1599; (c) J. Wan, C.-J. Zheng, M.-K. Fung, X.-K. Liu, C.-S. Lee, X.-H. Zhang, *J. Mater. Chem.,* 2012, **22**, 4502.

3 (a) Y. Liu, Z. Song and B. Yan, *Org. Lett.,* 2007, **9**, 409. (b) B. Yan and Y. Liu, *Org. Lett.,* 2007, **9**, 4323. (c) S. Chuprakov and V. Gevorgyan, *Org. Lett.,* 2007, **9**, 4463. (d) L. El Kaim, M. Gizolme, and L. Grimaud, *Synlett* 2007, 227. (e) S. Marchalin, J. Zuziova, K. Kadlec ikova, P. Safar, P. Baran, V. Dalla and A. Daich, *Tetrahedron Lett.,* 2007, **48**, 697. (f) Y. Liu, H-Y. Hu, Q-J. Liu, H-W. Hu and J.-

H. Xu, *Tetrahedron* 2007, **63**, 2024. (g) J. J. Li, J. J. Li, J. Li, A. K. Trehan, H. S. Wong, S. Krishnananthan, L. J. Kennedy, Q. Gao, A. Ng, J. A. Robl, B. Balasubramanian and B.-C. Chen, *Org. Lett.,* 2008, **10**, 2897. (h) L. Zhu, M. Vimolratana, S. P. Brown and J. C. Medina, *Tetrahedron Lett.,* 2008, **49**, 1768. (i) Y. Shang, M. Zhang, S. Yu, K. Ju, C. Wang and X. He, *Tetrahedron Lett.,* 2009, **50**, 6981. (j) Y. Bai, J. Zeng, J. Ma, B. K. Gorityala and X.-W. J. Liu, *Comb. Chem.,* 2010, **12**, 696. (k) D. Chernyak, C. Skontos and V. Gevorgyan, *Org. Lett.,* 2010, **12**, 3242. (l) P. Liu, C.-L. Deng, X. Lei and G.-Q. Lin, *Eur. J. Org. Chem,*. 2011, 7308. (m) H. Zhu, J. Stöckigt, Y. Yu and H. Zou, *Org. Lett.,* 2011, **13**, 2792. (n) L. H. Phun, J. Aponte-Guzman and S. France, *Angew. Chem., Int. Ed.,* 2012, **51**, 3198. (o) T. Aggarwal, S. Kumar, D. K. Dhaked, R. K. Tiwari, P. V. Bharatam and A. K. Verma, *J. Org. Chem.,* 2012, **77**, 8562. (p) Y. Yang, C. Xie, Y. Xie and Y. Zhang, *Org. Lett.,* 2012, **14**, 957. (q) J. H. Lee and I. Kim, *J. Org. Chem.,* 2013, **78**, 1283. (r) D. K. Friel, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.,* 2008, **130**, 9942. (s) J. Robertson, A. J. Tyrrell, P. T. Chovatia and S. Skerratt, *Tetrahedron Lett.,* 2009, **50**, 7141. (t) I. Kim and K. Kim, *Org. Lett.,* 2010, 12, 2500. (u) M. Murai, S. Kitabata, K. Okamoto and K. Ohe, *Chem. Commun.,* 2012, **48**, 7622. (v) A. R. H. Narayan and R. Sarpong, *Org. Biomol. Chem.,* 2012, **10**, 70. (w) H. Cho and I. Kim, *Tetrahedron* 2012, **68**, 5464. (x) S. T. Heller, T. Kiho, A. R. H. Narayan and R. Sarpong, *Angew. Chem., Int. Ed.,* 2013, **52**, 11129. (y) L.-H. Chung, C.-F. Yeung, D.-L. Ma, C.-H. Leung and C.-Y. Wong, *Organometallics* 2014, **33**, 3443.

4 (a) B. Liu, X. Qin, K. Li, Q. Guo, J. Lan and J. You, *Chem.-Eur. J.* 2010, **16**,11836; (b) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian and K. Fagnou, *J. Org. Chem.* 2011, **76**, 749; (c) T. P. Pathak and M. S. Sigman, *Org. Lett.* 2011, **13**, 2774; (d) L. Huang, T. Niu, J. Wu and Y. Zhang, *J. Org. Chem.* 2011, **76**, 1759; (e) Y. Yang, L. Chen, Z. Zhang and Y. Zhang, *Org. Lett.* 2011, **13**, 1342; (f) Y. Yang, K. Cheng and Y. Zhang, *Org. Lett.* **2009**, **11**, 5606; (g) H. Kim, K. Lee, S. Kim and P. H. Lee, *Chem. Commun.* 2010, **46**, 6341; (h) B. Zhao, *Org. Biomol. Chem.,* 2012, **10**, 7108; (i) V. Specowius, F. Bendrath, M. Winterberg, K. Ayub and P. Langer, *Adv. Synth. Catal.* 2012, **354**, 1163; (j) X.-C. Tan, Y. Liang, F.-P. Bao, H.-S. Wang and Y.-M Pan, *Tetrahedron* 2014, **70**, 6717.

5 M. Gao, J. Tian and A. Lei, *Chem.-Asian J.,* 2014, **9**, 2068.

6 L. Xiang, Y. Yang, X. Zhou, X. Liu, X. Li, X. Kang, R. Yan and G. Hang, *J. Org. Chem.,* 2014, **79**, 10641.

7 (a) Y. Zi, Z.-J. Cai, S.-Y. Wang, S.-J, Ji. *Org. Lett.,* **2014**, *16*, 3094. (b) Z.-J. Cai, S.-Y. Wang,S.-J, Ji. *Org. Lett.,* 2013, **15**, 5226. (c) K. Xu, Y. B. Hu, S. Zhang, Z. G. Zha and Z. Y. Wang, *Chem. Eur. J.* 2012, **18**, 9793. (d) Y. Z. Wu and Z. Y .Wang, *Chem. Commun*., 2011, **47**, 9513. (e) M. Lamani, K. R. Prabhu, *J. Org. Chem.,* 2011, **76**, 7938. (f) J. T. Zhang, D. P. Zhu, C. M. Yu, C. F. Wan and Z. Y. Wang, *Org. Lett.,* 2010, **12**, 2841. (g) C. F. Wan, L. F. Gao, Q. Wang, J. T. Zhang, Z. Y. Wang, *Org. Lett.,* 2010, **12**, 3902.

8 (a) M. Gao, Y. Yang, Y.-D. Wu, C. Deng, W.-M. Shu, D.-X Zhang, L.-P. Cao, N.-F. She and A.-X. Wu, *Org. Lett.* 2010, **12**, 4026; (b) Y.-P. Zhu, F.-C. Jia, M.-C. Liu and A.-X. Wu, *Org. Lett.* 2012, **14**, 4414; (c) W.-J. Xue, Y.-Q. Guo, F.-F. Gao, H.-Z. Li and A.-X. Wu, *Org. Lett.* 2013, **15**, 890; (d) Y.-P. Zhu, F.-C. Jia, M. -C. Liu and A.-X. Wu, *Org. Lett.,* 2012, **14**, 4414. (e) Z. He, W. Liu, Z. Li, *Chem. -Asian J.* 2011, **6**, 1340.

9 (a) R.-L. Yan, J. Luo, C.-X. Wang, C.-W. Ma, G.-S. Huang and Y.-M. Liang, *J. Org. Chem.,* 2010, **75**, 5395; (b) 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; (c) H. Yan, R. Yan, S. Yang, X. Gao, Y. Wang, G. Huang and Y. Liang, *Chem. - Asian J.,* 2012, **7**, 2028; (d) R. Yan, X. Liu, C. Pan, X. Zhou, X. Li, X. Kang and G. Huang, *Org. Lett.,* 2013, **15**, 4876. (e) R. Yan, X. Kang, X. Zhou, X. Li, X. Liu, L. Xiang, Y. Li, G. Huang, *J. Org. Chem*., 2014, **79**, 465. (f) R. Yan, X. Zhou, M. Li, X. Li, X. Kang, X. Liu, X.Huo, G. Huang, *RSC Adv.* 2014, **4**, 50369.

