RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 29424

Received 21st January 2015
Accepted 17th March 2015

DOI: 10.1039/c5ra01234a

www.rsc.org/advances

An I_2-catalyzed oxidative cyclization for the synthesis of indolizines from aromatic/aliphatic olefins and α-picoline derivatives†

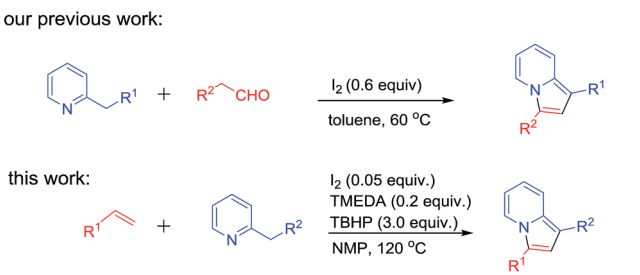
Likui Xiang, Fuming Zhang, Baohua Chen, Xiaobo Pang, Xiaodong Yang, Guosheng Huang and Rulong Yan*

A novel 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 bond formation in one pot.

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

To overcome some of the disadvantages associated with metal catalysts and complex substrates, a I_2/TBHP reaction system is an appropriate candidate for both academic and industrial communities for our transformation.[7] Iodine and olefins, as common and easily available substrates, have been widely used for constructing the scaffolds of heterocyclic compounds.[8] On the basis of our previous studies on the synthesis of heterocyclic compounds,[9] we envisaged that substituted indolizines could be realized from olefins and α-picoline derivatives *via* I_2-catalysis. 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 report interesting results from a direct I_2-catalyzed oxidative cyclization protocol for the synthesis of substituted indolizines with alkyl pyridines and aldehydes.

In order to improve the yield of **3aa**, different solvents were initially screened and NMP was found to be the best one for this reaction (Table 1, entry 3). After changing the amount of I_2, a higher yield was achieved when 0.05 equiv. of I_2 was used in the transformation. Then various oxidants were also evaluated for this reaction, and 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**

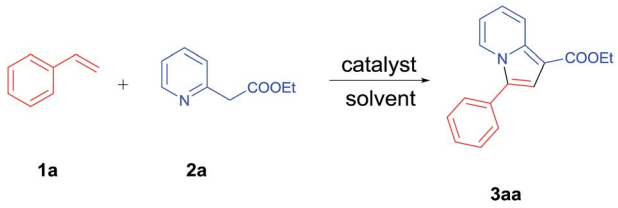


Scheme 1 The methods of synthesizing substituted indolizines.

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. E-mail: yanrl@lzu.edu.cn; Fax: +86-931-8912596

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/c5ra01234a

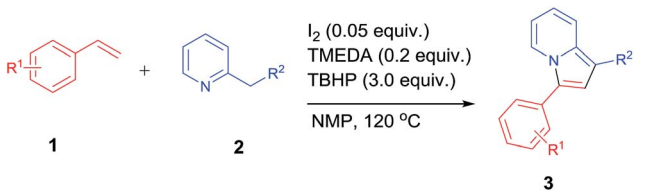
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (equiv.)	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-Phenanthroline	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.) and oxidant (3.0 equiv.) in 2 mL of solvent for 4 h at 120 °C. DMF = dimethyl formamide, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran, NMP = *N*-methyl-2-pyrrolidone. [b] Isolated yield.

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



Entry	1	R^1	2	R^2	Product	Yield (%)[b]
1	**1a**	H	**2a**	COOEt	**3aa**	74
2	**1b**	2-Me	**2a**	COOEt	**3ba**	71
3	**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.) and TBHP (3.0 equiv.) in 2 mL NMP for 4 h. [b] Isolated yield.

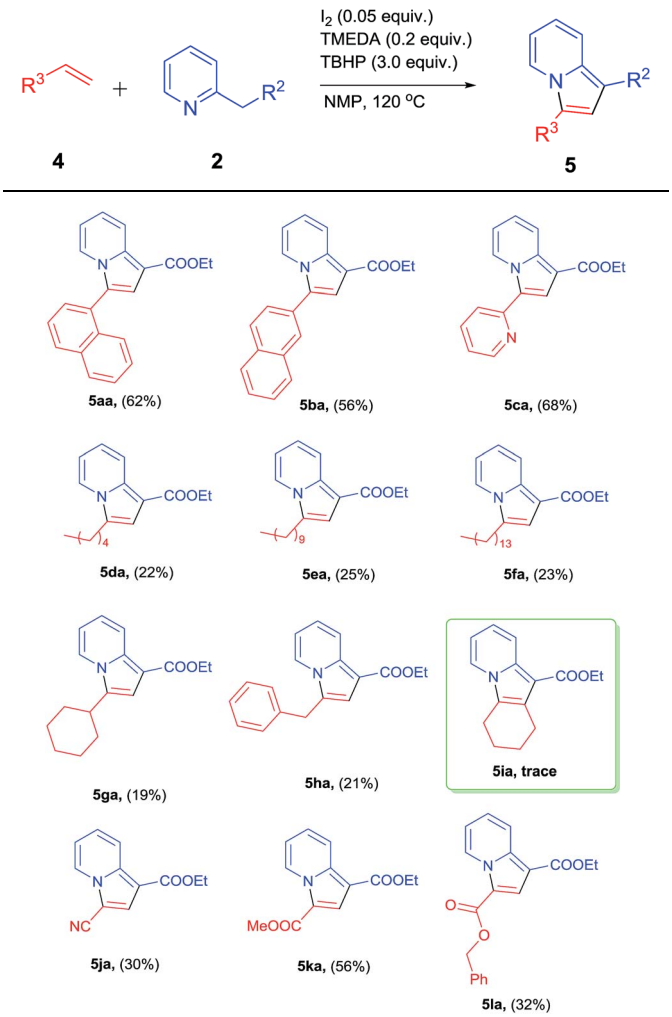
was increased to 74% when 20 mol% of TMEDA was employed as an additive (Table 1, entry 13). Moreover, I_2 played an important role in this reaction because no desired product was generated without I_2 (Table 1, entries 17 and 18).

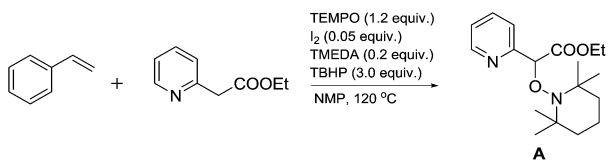
With the optimized conditions in hand, the scope in terms of the substituted styrenes and 2-pyridyl acetates/acetone/acetonitrile was examined and the results are illustrated in Table 2. It was gratifying to find that a variety of substituted styrenes could react with the 2-pyridyl acetates/acetonitrile smoothly and furnished the desired products in moderate yields. As shown in Table 2, the substituents on the aryl ring of the styrene did not have a certain influence on the formation of the products. In particular, the styrenes bearing an electron withdrawing group, such as F, Cl, Br, generated the desired products in slightly higher yields than the electron-donating ones. Moreover, when the substrate **2a** was changed to **2b** or **2c**, the substrates underwent efficient cyclization and the desired products were afforded in moderate yields. When 2-pyridylacetone was employed for this reaction, only a trace amount of the desired product was detected.

To further extend the substrate scope, we then paid attention to some more challenging alkenes to evaluate the procedure (Table 3). Gratifyingly, the alkenes with different functional groups displayed an efficient compatibility and produced the target products in moderate yields. Vinylnaphthalenes (**4a** and **4b**) and 2-vinylpyridine (**4c**) performed well and gave the expected products for this process. Specially, aliphatic alkenes could react under the optimized conditions and form the desired products, except for cyclohexene. Interestingly, even aliphatic alkenes bearing cyano and ester groups were well tolerated in this transformation and offered the target products in moderate yields.

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

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

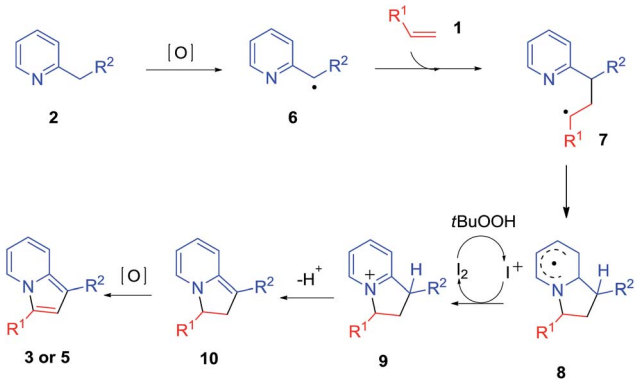




Scheme 2 Control experiment.

Based on the above experiments, a proposed mechanism is shown in Scheme 3. Initially, the substrate **2** generates a radical intermediate **6** under the optimized conditions. Then, **6** adds to the substrate **1** to afford radical intermediate **7**, which can be further cyclized to give intermediate **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 synthesize substituted indolizines, catalyzed by I_2. Substituted



Scheme 3 Proposed mechanism.

aromatic/aliphatic olefins and α-picoline derivatives all can be well tolerated in this transformation and generate the desired products in moderate yields.

Acknowledgements

This work was supported by the 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 and A. R. Mount, *Phys. Chem. Chem. Phys.*, 2011, **13**, 5235; (*b*) B. Liu, Z. Wang, N. Wu, M. Li, J. You and J. Lan, *Chem.–Eur. J.*, 2012, **18**, 1599; (*c*) J. Wan, C.-J. Zheng, M.-K. Fung, X.-K. Liu, C.-S. Lee and 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 and S.-J. Ji, *Org. Lett.*, 2014, **16**, 3094; (*b*) Z.-J. Cai, S.-Y. Wang and 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 and 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 and 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 and 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 and G. Huang, *J. Org. Chem.*, 2014, **79**, 465; (*f*) R. Yan, X. Zhou, M. Li, X. Li, X. Kang, X. Liu, X. Huo and G. Huang, *RSC Adv.*, 2014, **4**, 50369.