RSC Advances

PAPER

Cite this: *RSC Adv.*, 2020, **10**, 8348

Iodine-catalyzed convergent aerobic dehydro-aromatization toward benzazoles and benzazines†

Xiaolong Tuo, Shanping Chen,* Pingyu Jiang, Penghui Ni, Xiaodong Wang and Guo-Jun Deng *

Received 27th December 2019
Accepted 15th February 2020

DOI: 10.1039/c9ra10964a

rsc.li/rsc-advances

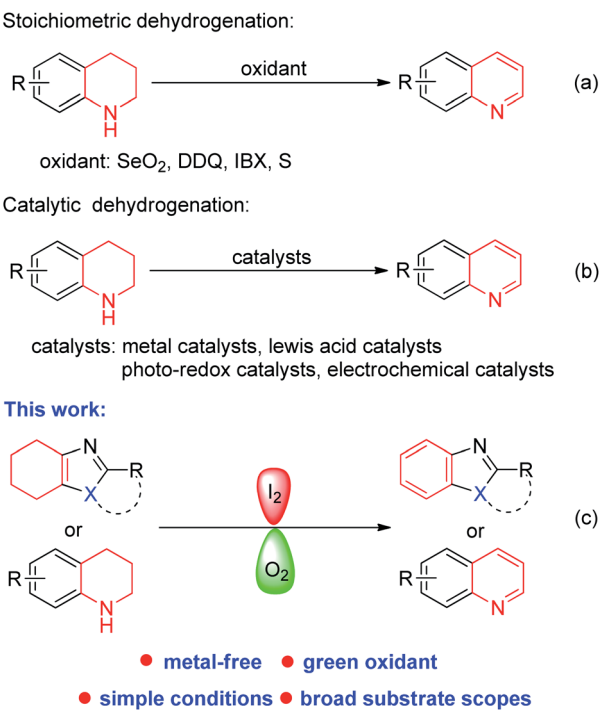
An iodine-catalyzed aerobic dehydro-aromatization has been developed, providing straightforward and efficient access to various benzoazoles and benzoazines. The present transition-metal-free protocol enables the dehydro-aromatization of tetrahydrobenzazoles and tetrahydroquinolines with molecular oxygen as the green oxidant, along with some other N-heterocycles. Hence, a broad range of heteroaromatic compounds are generated in moderate to good yields under facile reaction conditions.

Introduction

Benzazoles and benzazines have unique pharmacological and biological activities and thus have many applications in natural products and pharmaceutical drugs.[1–3] As a result, chemical researchers have been actively seeking new methodologies to synthesize these compounds. In recent years, dehydrogenative aromatization has emerged as a direct and efficient approach to access heteroaromatic compounds, especially N-heterocycles. This strategy produces a series of benzazines with high value[4] and continues to be an attractive and significant research object in organic synthesis.

The direct dehydro-aromatization methods were generally achieved by using stoichiometric oxidants, such as SeO_2, DDQ, *o*-iodoxybenzoic acid (IBX) and sulfur (Scheme 1a).[5,6] Recently, transition metal catalysts combined with oxygen as the sole sacrificial reagent were used to enable oxidative dehydrogenative aromatization, such as Au, Pt, Pd, Ru, Fe, and Co.[7–9] On the other hand, in view of the atom-economy requirement and potential application for hydrogen storage, Ir, Ru, Fe and Co catalyst were used for the acceptorless dehydrogenation reactions of N-heterocycles.[10–12] However, due to the involvement of transition metals and other specialized catalysts or amounts of oxidants, these dehydrogenation protocols are often expensive or not environmentally friendly. In recent years, Lewis acids,[13] photoredox catalysis,[14] electrocatalysis[15] and graphene oxide (GO)[16] were used for the same goal (Scheme 1b). In addition, potassium *tert*-butoxide[17] and elemental sulfur[18] also could promote the dehydrogenation process. However, most of these methods are mainly suitable for dehydro-aromatization of N-heterocycles. Hence, developing a convergent catalytic system which can be employed for dehydro-aromatization of both carbocycles and N-heterocycles to afford a diversity of heteroaromatic compounds is highly desirable.

Our group has been focusing on synthesizing aromatic heterocyclic compounds, using cyclohexanones as the aryl source *via* a dehydrogenative aromatization sequence.[19,20] In our recent research, cyclohexanones coupled with amines to form tetrahydrobenzimidazoles, which could not be dehydrogenated to produce heteroaromatic compounds under these conditions.[21] As a follow up study, herein, we describe an iodine



Scheme 1 Kinds of dehydrogenative aromatization reactions.

Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China. E-mail: spchen@xtu.edu.cn; gjdeng@xtu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra10964a

catalyzed dehydro-aromatization reaction using molecular oxygen as the green oxidant toward various benzazoles and benzazines (Scheme 1c).

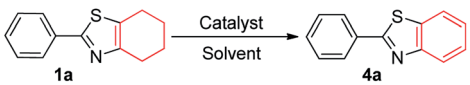
Results and discussion

We commenced our studies by choosing 2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole (**1a**) as the model substrate. The desired product **4a** was afforded in 36% in the presence of KI and oxygen (Table 1, entry 1). Then, a series of iodide-containing reagents such as NaI, NIS, elemental iodine, ICl and $NaIO_4$ were screened (entries 2–6).[22] The best reaction yield was achieved when elemental iodine was added as the catalyst (entry 4). A control experiment showed that trace of desired product was obtained in the absence of iodine reagent (entry 7). Subsequently, several solvents were tested. All of them did not give a higher yield (entries 8–13). The yield was up to 79% when *o*-dichlorobenzene (*o*-DCB) and toluene were used as the mixed solvent (entry 14). When the reaction atmosphere was changed to air, the reaction yield dramatically decreased (entry 15). A lower yield was obtained when the reaction was performed at 140 °C (entry 16).

With the optimized conditions in hand, we explored the scope of this dehydrogenative aromatization reaction. The model reaction afforded the target product **4a** in 75% isolated yield, and 68% isolated yield could be achieved in a gram-scale reaction. The corresponding products were obtained in moderate to good yields, when 2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole substrates bearing with various substituents, such as alkyl, aryl, methoxy and halogen (**4b–4i**). Bulky 1-(naphthalen-1-yl)-4,5,6,7-tetrahydrobenzo[*d*]thiazole and 2-(naphthalen-1-yl)-4,5,6,7-tetrahydrobenzo[*d*]thiazole could also react well to afford the target products in good yields (**4j**, **4k**). The steric effect of groups was not obvious on the reaction and the corresponding products were obtained in 62–74% yields when the carbocycle with an substituent (**4l–4n**). The desired product **4o** could be obtained in 56% yield when 1-benzyl-2-phenyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imida-zole was used as the substrate. Regrettably, 2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]oxazole could not be dehydrogenated under the standard condition (**4p**). Subsequently, we investigated the dehydrogenation of tetracycle-fused system. Benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole **5a** could be smoothly generated in 71% yield under the standard conditions when 7,8,9,10-tetrahydrobenzo[*d*]benzo[4,5]imida-zo[2,1-*b*]thiazole was used as the substrate. The substrates bearing a substituent such as methyl and halogen on the benzene ring afforded the corresponding product in 63–70% yields (**5b–5d**). The dehydrogenative products were gave in 64–71% yields when carbocycle was decorated by an alkyl or aryl substituent (**5e**, **5f**) (Tables 2 and 3).

To further extend the scope of the substrates, we tested a variety of N-heterocycles under the standard reaction condition. Fortunately, most of them could give the desired products in moderate to good yields. Quinoline **6a** was generated in 67% yield when 1,2,3,4-tetrahydroquinoline was used as the substrate. Tetrahydroquinolines with a methyl located at 2-, 3-, 4-, or 8-position could afford the corresponding dehydrogenation products in good yields (**6b–6e**). Strong electron-

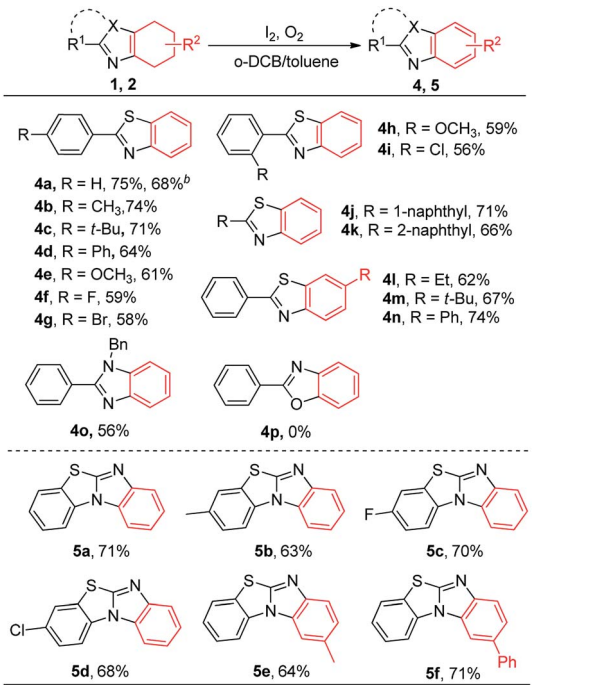
Table 1 Optimization reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	KI	*o*-DCB	36%
2	NaI	*o*-DCB	39%
3	NIS	*o*-DCB	52%
4	I_2	*o*-DCB	71%
5	$NaIO_4$	*o*-DCB	68%
6	ICl	*o*-DCB	67%
7	—	*o*-DCB	Trace
8	I_2	Chlorobenzene	51%
9	I_2	Toluene	55%
10	I_2	1,4-Dioxane	23%
11	I_2	DMSO	Trace
12	I_2	NMP	ND
13	I_2	DMA	ND
14[c]	I_2	*o*-DCB/toluene	79% (75%)[f]
15[c,d]	I_2	*o*-DCB/toluene	48%
16[c,e]	I_2	*o*-DCB/toluene	53%

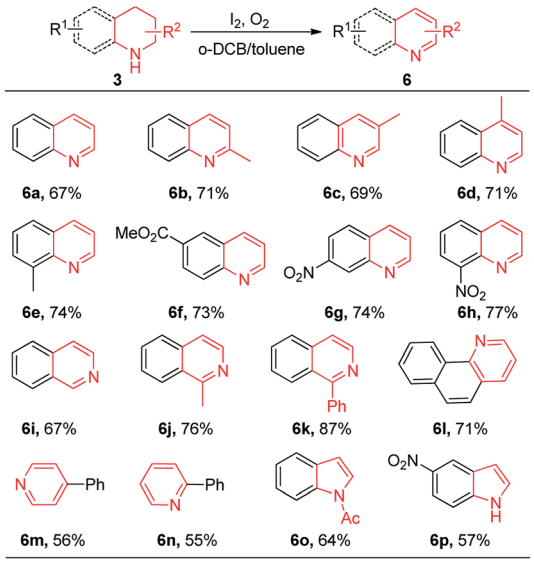
[a] Reaction conditions: **1a** (0.2 mmol), catalyst (20 mol%), solvent (0.8 mL), 160 °C, under O_2 (sealed tube), 30 h. [b] GC yield. [c] *o*-DCB/toluene (0.8 mL/0.2 mL). [d] Under air. [e] At 140 °C. [f] Isolated yield. *o*-DCB:*o*-dichlorobenzene, ND: not detected.

Table 2 Dehydro-aromatization of tetrahydrobenzazoles[a]

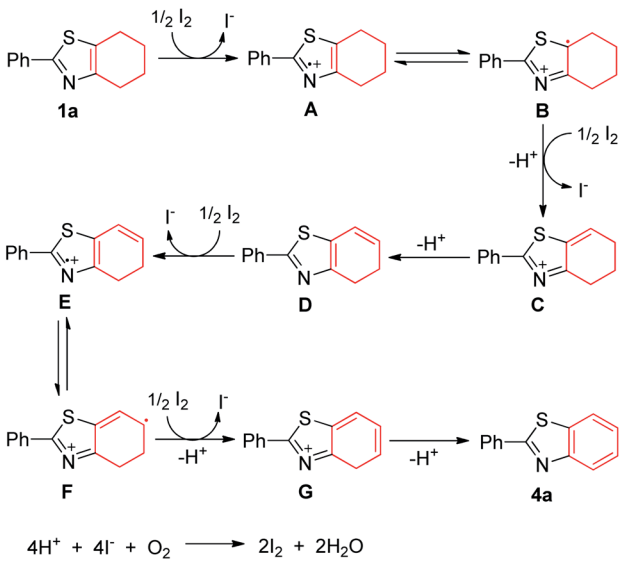


[a] Conditions: **1** or **2** (0.2 mmol), I_2 (20 mol%), *o*-DCB/toluene (0.8 mL/0.2 mL), 160 °C, 30 h, under O_2 (sealed tube), isolated yield. [b] 6 mmol scale.

Table 3 Dehydro-aromatization of N-heterocycles[a]



[a] Conditions: **3** (0.2 mmol), I_2 (20 mol%), *o*-DCB/toluene (0.8 mL/0.2 mL), 160 °C, 30 h, under O_2, isolated yield.



Scheme 2 Possible reaction mechanism.

withdrawing groups, such as ester and nitro groups, attached at tetrahydroquinoline substrates were well tolerated to give the target products (**6f–6h**). The dehydrogenation reactions of 1,2,3,4-tetrahydroisoquinoline smoothly proceeded to give the corresponding isoquinoline products in 67–87% yields (**6i–6k**). Benzo[*h*]quinoline **6l** was produced in 71% yield. In addition, 4-phenylpiperidine and 2-phenylpiperidine could be oxidized to form pyridine products in moderate yields under standard conditions (**6m**, **6n**). Furthermore, indole products could be obtained in good yields when 1-(indolin-1-yl)ethanone and 5-nitroindoline were used (**6o**, **6p**).

On the basis of relevant literatures,[23] a possible reaction mechanism is illustrated in Scheme 2. Initially, nitrogen-centered radical **A** is formed *via* single-electron oxidation process from **1a** in the presence of elemental iodide, and elemental iodide converts into iodine ion. Tautomerization of **A** produces intermediate **B**. Subsequent single-electron oxidation and deprotonation of **B** generates intermediate **C**, which can be further transformed into intermediate **D** *via* a deprotonation. Meanwhile, the second single-electron oxidative dehydrogenation of **D** affords the intermediate **G**, followed by a deprotonation to provide the desired product **4a**. The iodide anion is oxidized to form iodine in the presence of oxygen.

Conclusions

In conclusion, we have developed a direct dehydro-aromatization of tetrahydrobenzazoles and N-heterocycles, providing a straightforward and efficient approach to a variety of benzazoles and benzazines. The present protocol is achieved by use of elemental iodine as the catalyst and molecular oxygen as the green oxidant, which could produce a broad range of products in moderate to good yields under facile transition-metal-free conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21871226, 21572194, 21372187), the Collaborative Innovation Center of New Chemical Technologies for Environmental Benignity and Efficient Resource Utilization.

Notes and references

1 (*a*) M. O. Chaney, P. V. Demarco, N. D. Jones and J. L. J. Occolowitz, *J. Am. Chem. Soc.*, 1974, **96**, 1932; (*b*) M. K. Sahoo, G. Jaiswal, J. Rana and E. Balaraman, *Chem.–Eur. J.*, 2017, **23**, 14167; (*c*) O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi and S. Bawa, *Eur. J. Med. Chem.*, 2015, **97**, 871.

2 (*a*) N. Kumar, M. Alamgir, D. St and C. Black, *Heterocycl. Chem.*, 2007, **9**, 87; (*b*) M. E. Doyle and J. M. Egan, *Pharmacol. Rev.*, 2003, **55**, 105; (*c*) S. Meidute-Abaraviciene, H. Mosen, I. Lundquist and A. Salehi, *Acta Physiol.*, 2009, **195**, 375.

3 (*a*) D. K. Kahlon, T. A. Lansdell, J. S. Fisk and J. Tepe, *Bioorg. Med. Chem.*, 2009, **17**, 3093; (*b*) F. Touzeau, A. Arrault, G. Guillaumet, E. Scalbert, B. Pfeiffer, M.-C. Rettori, P. Renard and J.-Y. Merour, *J. Med. Chem.*, 2003, **46**, 1962; (*c*) A. Masajtis-Zagajewska, J. Majer and M. Nowicki, *Hypertens. Res.*, 2010, **33**, 348.

4 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.

5 (*a*) J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y. L. Wong, H. J. Chen, A. K. Courtney and S. F. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 8584; (*b*) K. C. Nicolaou, C. J. N. Manthison and T. Montagnon, *J. Am. Chem. Soc.*, 2004, **126**, 5192.

6 (*a*) M. Zhao, L. Bi, W. Wang, C. Wang, M. Baudy-Floćh, J. Ju and S. Peng, *Bioorg. Med. Chem.*, 2006, **14**, 6998; (*b*) M. Cain, O. Campos, F. Guzman and J. M. Cook, *J. Am. Chem. Soc.*, 1983, **105**, 907; (*c*) K. C. Nicolaou, C. J. N. Mathison and T. Montagnon, *Angew. Chem., Int. Ed.*, 2003, **42**, 4077.

7 (*a*) M. H. So, Y. Liu, C. M. Ho and C. M. Che, *Chem.–Asian J.*, 2009, **4**, 1551; (*b*) D. V. Jawale, E. Gravel, N. Shah, V. Dauvois, H. Li, I. N. Namboothiri and E. Doris, *Chem.–Eur. J.*, 2015, **21**, 7039; (*c*) D. Ge, L. Hu, J. Wang, X. Li, F. Qi, J. Lu, X. Cao and H. Gu, *ChemCatChem*, 2013, **5**, 2183.

8 (*a*) S. Furukawa, A. Suga and T. Komatsu, *Chem. Commun.*, 2014, **50**, 3277; (*b*) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc.*, 2014, **136**, 11910.

9 (*a*) X. Cui, Y. Li, S. Bachmann, M. Scalone, A.-E. Surkus, K. Junge, C. Topf and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 10652; (*b*) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc.*, 2014, **136**, 506; (*c*) A. V. Iosub and S. S. Stahl, *Org. Lett.*, 2015, **17**, 4404.

10 (*a*) R. Yamaguchi, C. Ikeda, Y. Takahashi and K. Fujita, *J. Am. Chem. Soc.*, 2009, **131**, 8410; (*b*) K. Fujita, Y. Tanaka, M. Kobayashi and R. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 4829; (*c*) J. Wu, D. Talwar, S. Johnston, M. Yan and J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 6983; (*d*) R. Xu, S. Chakraborty, H. Yuan and W. D. Jones, *ACS Catal.*, 2015, **5**, 6350.

11 (*a*) S. Muthaiah and S. H. Hong, *Adv. Synth. Catal.*, 2012, **354**, 3045; (*b*) S. Chakraborty, W. W. Brennessel and W. D. Jones, *J. Am. Chem. Soc.*, 2014, **136**, 8564; (*c*) G. Jaiswal, V. G. Landge, D. Jagadeesan and E. Balaraman, *Nat. Commun.*, 2017, **8**, 2147.

12 (*a*) R. H. Crabtree, *ACS Sustainable Chem. Eng.*, 2017, **5**, 4491; (*b*) Y. H. Han, Z. Y. Wang, R. R. Xu, W. Zhang, W. X. Chen, L. R. Zheng, J. Zhang, J. Luo, K. L. Wu, Y. Q. Zhu, C. Chen, Q. Peng, Q. Liu, P. Hu, D. S. Wang and Y. Li, *Angew. Chem., Int. Ed.*, 2018, **57**, 11262; (*c*) C. Deraedt, R. Ye, W. T. Ralston and F. D. Toste, *J. Am. Chem. Soc.*, 2017, **139**, 18084.

13 (*a*) A. F. G. Maier, S. Tussing, T. Schneider, U. Flörke, Z.-W. Qu, S. Grimme and J. Paradies, *Angew. Chem., Int. Ed.*, 2016, **55**, 12219; (*b*) M. Kojima and M. Kanai, *Angew. Chem., Int. Ed.*, 2016, **55**, 12224.

14 (*a*) S. Kato, Y. Saga, M. Kojima, H. Fuse, S. Matsunaga, A. Fukatsu, M. Kondo, S. Masaoka and M. Kanai, *J. Am. Chem. Soc.*, 2017, **139**, 2204; (*b*) K.-H. He, F.-F. Tan, C.-Z. Zhou, G.-J. Zhou, X.-L. Yang and Y. Li, *Angew. Chem., Int. Ed.*, 2017, **56**, 3080; (*c*) M. F. Zheng, J. L. Shi, T. Yuan and X. C. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 5487; (*d*) S. Chen, Q. Wan and A. K. Badu-Tawiah, *Angew. Chem., Int. Ed.*, 2016, **55**, 9345; (*e*) F. Su, S. C. Mathew, L. Mçhlmann, M. Antonietti, X. Wang and S. Blechert, *Angew. Chem., Int. Ed.*, 2011, **50**, 657.

15 Y. Wu, H. Yi and A. Lei, *ACS Catal.*, 2018, **8**, 1192.

16 J. Y. Zhang, S. Y. Chen, F. F. Chen, W. S. Xu, G.-J. Deng and H. Gong, *Adv. Synth. Catal.*, 2017, **359**, 2358.

17 T. T. Liu, K. K. Wu, L. D. Wang and Z. K. Yu, *Adv. Synth. Catal.*, 2019, **361**, 3958.

18 T. B. Nguyen and P. Retailleau, *Adv. Synth. Catal.*, 2018, **360**, 2389.

19 (*a*) X. X. Cao, X. F. Cheng, Y. Bai, S. W. Liu and G.-J. Deng, *Green Chem.*, 2014, **16**, 4644; (*b*) Y. F. Liao, Y. Peng, H. G. Qi, G.-J. Deng, H. Gong and C.-J. Li, *Chem. Commun.*, 2015, **51**, 1031; (*c*) J. J. Chen, G. Z. Li, Y. J. Xie, Y. F. Liao, F. H. Xiao and G.-J. Deng, *Org. Lett.*, 2015, **17**, 5870.

20 (*a*) J. Wu, Y. J. Xie, X. G. Chen and G.-J. Deng, *Adv. Synth. Catal.*, 2016, **358**, 3206; (*b*) Y. J. Xie, J. Wu, X. G. Che, Y. Chen, H. W. Huang and G.-J. Deng, *Green Chem.*, 2016, **18**, 667; (*c*) S. P. Chen, L. R. Wang, J. Zhang, Z. R. Hao, H. W. Huang and G.-J. Deng, *J. Org. Chem.*, 2017, **82**, 11182.

21 (*a*) Y. J. Xie, X. G. Chen, Z. Wang, H. W. Huang, B. Yi and G.-J. Deng, *Green Chem.*, 2017, **19**, 4294; (*b*) X. G. Chen, Z. Wang, H. W. Huang and G.-J. Deng, *Adv. Synth. Catal.*, 2018, **360**, 4017.

22 (*a*) Y. Su, X. J. Zhou, C. L. He, W. Zhang, X. Ling and X. Xiao, *J. Org. Chem.*, 2016, **81**, 4981; (*b*) S. Tang, K. Liu, Y. Long, X. T. Qi, Y. Lan and A. W. Lei, *Chem. Commun.*, 2015, **51**, 8769; (*c*) H. Cao, J. W. Yuan, C. Liu, X. Q. Hu and A. W. Lei, *RSC Adv.*, 2015, **5**, 41493; (*d*) W.-H. Bao, M. He, J.-T. Wang, X. Peng, M. Sung, Z. L. Tang, S. Jiang, Z. Cao and W.-M. He, *J. Org. Chem.*, 2019, **84**, 6065.

23 (*a*) V. Humne, Y. Dangat, K. Vanka and P. Lokhande, *Org. Biomol. Chem.*, 2014, **12**, 4832; (*b*) J. Zhao, H. Huang, W. Wu, H. Chen and H. Jiang, *Org. Lett.*, 2013, **15**, 2604; (*c*) S. P. Chen, Y. X. Li, P. H. Ni, B. C. Yang, H. W. Huang and G.-J. Deng, *J. Org. Chem.*, 2017, **82**, 2935.