ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 13367

Received 3rd October 2018,
Accepted 2nd November 2018

DOI: 10.1039/c8cc07905f

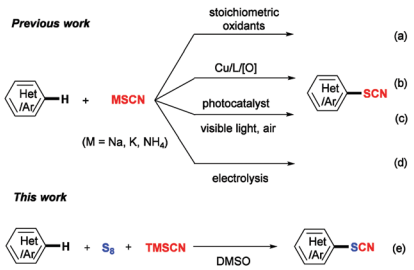
rsc.li/chemcomm

Catalyst and additive-free regioselective oxidative C–H thio/selenocyanation of arenes and heteroarenes with elemental sulfur/selenium and TMSCN†

Chengtao Feng,[a] Ya Peng,[a] Guangrong Ding,[a] Xiangxiao Li,[a] Chang Cui[b] and Yizhe Yan *[bc]

A regioselective oxidative C–H thio/selenocyanation of arenes and heteroarenes with TMSCN and elemental sulfur/selenium was demonstrated under catalyst-free and additive-free conditions. Dimethyl sulfoxide (DMSO) was employed as the mild oxidant as well as the solvent. The reaction is operationally simple and scalable with a broad substrate scope.

Organosulfur compounds are an important class of molecules due to their broad biological activities.[1] The construction of carbon–sulfur bonds is an important way to prepare organosulfur compounds. Much effort has been made towards the formation of carbon–sulfur bonds *via* direct C–H functionalization, such as trifluoromethylthiolation, thiolation and sulfonylation.[2] Among them, direct oxidative thiocyanation of arene C–H bonds is a facile method for the introduction of sulfur-containing groups. The thiocyanation product as a useful intermediate could readily be converted into other valuable sulfur-containing compounds, such as thiophenols, sulfonyl cyanides, *etc.*[3] Conventionally, the oxidative thiocyanation of arenes and heteroarenes was realized using thiocyanate salts, which mainly derived from sulfur and cyanate, as thiocyanation reagents in the presence of various chemical oxidants, such as hypervalent iodine reagents,[4] $K_2S_2O_8$,[5] oxone,[6] $Mn(OAc)_3$,[7] or other oxidants[8] (Scheme 1a). However, the use of stoichiometric oxidants, the narrow substrate scope and the generation of toxic wastes limited their further application. Recently, copper-catalyzed,[9] visible light-promoted,[10] and electrochemical[11] oxidative thiocyanation reactions have been developed (Scheme 1b–d). In these reactions, although oxygen or electrons were used as a green oxidant, a catalyst or electrolyte was required and thiocyanate salts were still used as thiocyanation reagents.



Scheme 1 Strategies for oxidative thiocyanation of arenes and heteroarenes.

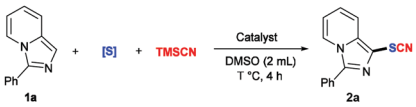
Elemental sulfur is one of the most important raw materials of the modern chemical industry in the preparation of black gunpowder, the vulcanization of rubber and the synthesis of sulfuric acid. Over the last several years, the application of elemental sulfur as a readily available and green sulfur source for the synthesis of sulfur-containing compounds has attracted much attention.[12] However, the use of elemental sulfur for C–H thiocyanation has not been reported yet. In continuation of our efforts on metal-free C–H functionalization,[13] herein we report a metal-free regioselective oxidative C–H thiocyanation of arenes and heteroarenes with elemental sulfur and TMSCN as a novel combined thiocyanation source (Scheme 1e). This reaction avoids the use of any catalyst and additive, providing a green and operationally simple method for the synthesis of thiocyanation products.

Initially, we began our study with the reaction of 1 equiv. of 3-phenylimidazo[1,5-*a*]pyridine (**1a**) as the model substrate, 2 equiv. of precipitated sulfur and trimethylsilyl cyanide as the combined thiocyanation source, and 20 mol% of CuI as the catalyst. When the reaction mixture was heated in 2 mL of DMSO at 90 °C for 24 h, 3-phenyl-1-thiocyanatoimidazo[1,5-*a*]-pyridine **2a** was obtained in 92% yield (Table 1, entry 1). When other copper catalysts were used as the catalysts, **2a** was obtained in slightly low yields compared with CuI (Table 1, entries 2–9). To our surprise, the absence of copper catalyst

[a] *School of Chemical Engineering, Anhui University of Science and Technology, Huainan, 232001, P. R. China*
[b] *School of Food and Biological Engineering, Zhengzhou University of Light Industry, Zhengzhou, 450000, P. R. China. E-mail: yanyizhe@mail.ustc.edu.cn*
[c] *Henan Key Laboratory of Cold Chain Food Quality and Safety Control, Zhengzhou, 450000, China*

† Electronic supplementary information (ESI) available: Experimental procedures and spectral data and copies of NMR spectra for all products. See DOI: 10.1039/c8cc07905f

Table 1 Optimization of reaction conditions[a]

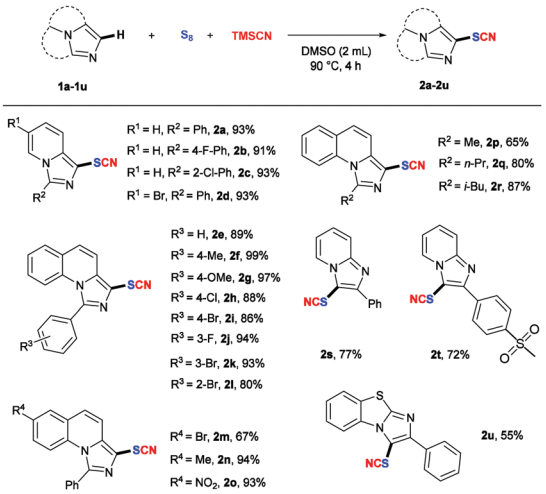


Entry	Catalyst	S source	Solvent	Yield[b] (%)
1	CuI	Precipitated sulfur	DMSO	92
2	CuBr	Precipitated sulfur	DMSO	91
3	Cu_2O	Precipitated sulfur	DMSO	80
4	CuCl	Precipitated sulfur	DMSO	90
5	$CuCl_2$	Precipitated sulfur	DMSO	84
6	$Cu(OAc)_2{\cdot}H_2O$	Precipitated sulfur	DMSO	82
7	$CuSO_4$	Precipitated sulfur	DMSO	72
8	$CuCO_3$	Precipitated sulfur	DMSO	60
9	$CuBr_2$	Precipitated sulfur	DMSO	86
10		**Precipitated sulfur**	**DMSO**	**93**
11		Sublimed sulfur	DMSO	84
12		Na_2S	DMSO	n.d.
13		CH_3CSNH_2	DMSO	n.d.
14		Precipitated sulfur	DMF	n.d.
15		Precipitated sulfur	CH_3CN	n.d.
16		Precipitated sulfur	1,4-Dioxane	n.d.
17		Precipitated sulfur	EtOH	n.d.
18		Precipitated sulfur	Toluene	n.d.
19[c]		Precipitated sulfur	DMSO	83
20[d]		Precipitated sulfur	DMSO	85

[a] Reaction conditions: **1a** (0.2 mmol), S source (2 equiv., 0.4 mmol), TMSCN (2 equiv., 0.4 mmol), catalyst (20 mol%, 0.04 mmol), DMSO (2 mL), 90 °C, 4 h; n.d. = not detected. [b] Isolated yield. [c] 80 °C. [d] 100 °C.

resulted in an increase of the yield (Table 1, entry 10). Among the examination of various sulfur sources, such as sublimed sulfur, Na_2S and thioacetamide, only sublimed sulfur afforded **2a** in a lower 84% yield (Table 1, entries 11–13). Notably, when other solvents were used instead of DMSO, no **2a** was detected, indicating that DMSO might play an important role in this reaction (Table 1, entries 14–18). In addition, increasing or reducing the reaction temperature obviously decreased the reaction yields (Table 1, entries 19 and 20). Therefore, the optimal conditions were established as described in entry 10.

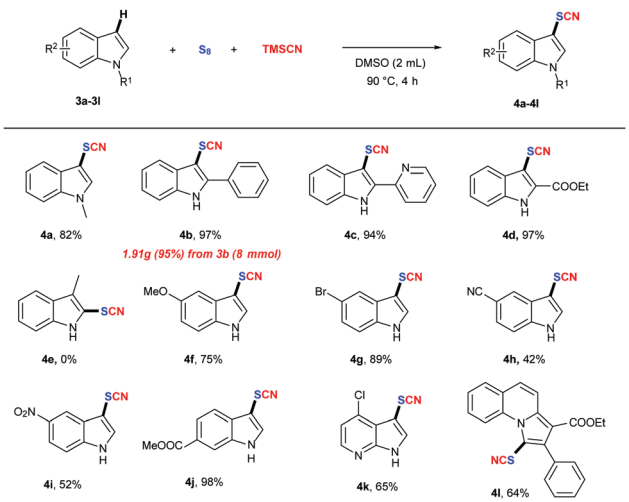
Under the optimal reaction conditions, the generality of the synthetic protocol for imidazo-fused heterocycles **1** was investigated (Scheme 2). First, various 3-phenylimidazo[1,5-*a*]pyridines (**1a–1d**) could be employed in this reaction, regioselectively affording 1-thiocyano products **2a–2d** in excellent yields. Subsequently, imidazo[1,5-*a*]quinolines (**1e–1r**) were also suitable for this protocol due to the similarity of their chemical structure with imidazo-[1,5-*a*]pyridines. 1-Phenylimidazo[1,5-*a*] quinolines (**1e–1l**) bearing electron-donating groups (Me and OMe) or electron-deficient ones (F, Cl, and Br) on the phenyl ring could produce the 3-thiocyano products **2e–2l** in good yields, whereas the electron-donating groups (**1f** and **1g**) gave higher yields than the electron-deficient ones (**1h–1l**). It was noted that the steric-hindrance effect of the group on the reaction yields was not obvious due to the far reaction site (**2j** and **2l**). When Br, Me, or NO_2 as an R^4 substituent was introduced into the 7-position of 1-phenylimidazo[1,5-*a*]quinoline, the desired 3-thiocyano products **2m–2o** were also obtained in 67–94% yields. To our delight, 1-alkyl-imidazo[1,5-*a*]quinolines also generated the desired products **2p–2r** in 65–87% yields. Moreover, the corresponding



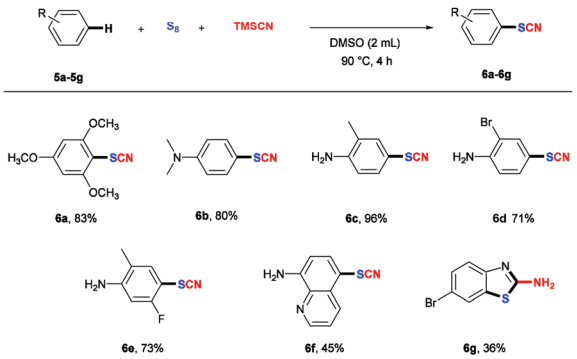
Scheme 2 C–H thiocyanation of imidazo-fused heterocycles. Reaction conditions: **1** (0.2 mmol), S_8 (2 equiv., 0.4 mmol), TMSCN (2 equiv., 0.4 mmol), DMSO (2 mL), 90 °C, 4 h.

3-thiocyano product **2s** was obtained in 77% yield with 2-phenylimidazo[1,2-*a*]pyridine (**1s**) as the substrate. Notably, 2-(4-(methylsulfonyl)phenyl)imidazo[1,2-*a*]pyridine (Zolimidine, **1t**) as a gastroprotective drug for peptic ulcer and gastroesophageal reflux disease could afford **2t** in 72% yield. In addition, 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (**1u**) as the substrate could afford 3-thiocyano product **2u** in moderate yield.

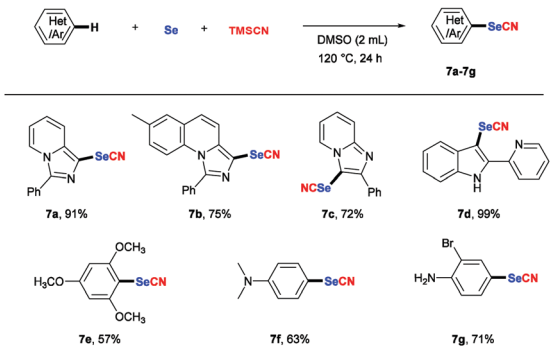
Subsequently, we expected to realize the regioselective thiocyanation of indoles **3** with this synthetic protocol (Scheme 3). The corresponding 3-thiocyano product **4a** was obtained in 82% yield with *N*-methylindole (**3a**) as the substrate. Moreover, the substrate scope of free indoles was also investigated. The reaction of indoles bearing a phenyl, pyridine-2-yl or ester group at the C2 position gave the corresponding products **4b–4d** in 97%, 94% or 97%, respectively, which suggested that this protocol was not obviously affected by steric hindrance.



Scheme 3 C–H thiocyanation of indoles. Reaction conditions: **3** (0.2 mmol), S_8 (2 equiv., 0.4 mmol), TMSCN (2 equiv., 0.4 mmol), DMSO (2 mL), 90 °C, 4 h.



Scheme 4 C–H thiocyanation of arenes. Reaction conditions: **5** (0.2 mmol), S_8 (2 equiv., 0.4 mmol), TMSCN (2 equiv., 0.4 mmol), DMSO (2 mL), 90 °C, 4 h.



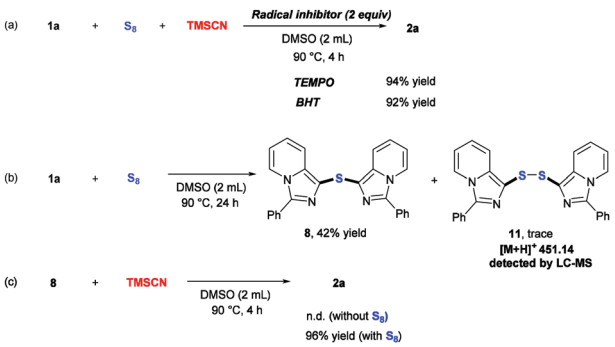
Scheme 5 C–H selenocyanation of arenes and heteroarenes. Reaction conditions: substrates (0.2 mmol), Se (2 equiv., 0.4 mmol), TMSCN (2 equiv., 0.4 mmol), DMSO (2 mL), 120 °C, 24 h.

The reaction of 3-methylindole (**3e**) failed, indicating an excellent regioselectivity of the C3 position. The reactions of indoles bearing electron-donating (5-OMe) or electron withdrawing groups (5-Br, 5-CN, 5-NO_2 and 6-COOMe) on the phenyl ring proceeded smoothly, affording the 3-thiocyano products **4f–4j** in 42–98% yields. Importantly, the presence of the Br, CN, NO_2 and COOMe groups provides potential for further derivatization. Furthermore, 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**3k**) also gave **4k** in 65% yield. In addition, ethyl 2-phenylpyrrolo[1,2-*a*]quinoline-3-carboxylate (**3l**) containing a pyrrole unit could also be tolerant in this reaction, affording the corresponding product **4l** in 64% yield. Notably, the gram-scale synthesis of **4b** was successfully achieved with a yield of 95%.

Then the regioselective thiocyanation of electron-rich arenes was realized using this synthetic protocol (Scheme 4). First, the thiocyanation of 1,3,5-trimethoxybenzene (**5a**) could produce 1,3,5-trimethoxy-2-thiocyanatobenzene (**6a**) in 83% yield under standard conditions. Moreover, using *N*,*N*-dimethylaniline (**5b**) as the substrate, 4-thiocyano product **6b** was obtained in 80% yield. Expectedly, the reaction of free anilines bearing Me and Br at the *ortho* position (**5c–5e**) also gave the 4-thiocyano products **6c–6e** in 71–96 yields. Similarly, when quinolin-8-amine (**5f**) was used as the substrate, 5-thiocyano product **6f** was obtained in low yield. Interestingly, the reaction of 4-bromoaniline (**5g**) did not generate the 2-thiocyano product but gave 6-bromobenzo[*d*]thiazol-2-amine (**6g**) in 36% yield through a further intramolecular cyclization.

Organic selenocyanates are also an important class of compounds because of their broad range of bioactivities such as antioxidative, antitumor activities, *etc*.[14] Encouraged by the results above, we expected to realize regioselective selenocyanation using elemental selenium and TMSCN as a novel selenocyanation source. To our delight, when various heterocycles (**1a**, **1n**, **1s** and **3c**) and arenes (**5a**, **5b** and **5d**) were employed as the substrates, the desired selenocyanation products **7a–7g** were obtained with the same regioselectivity to the thiocyanation process in moderate to excellent yields at 120 °C (Scheme 5).

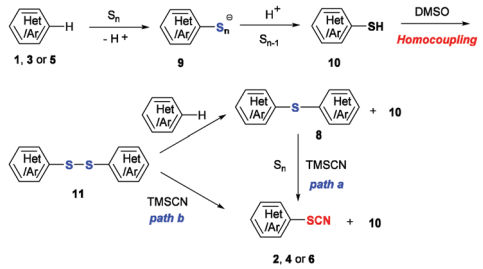
To gain insight into the mechanism, several control experiments were carried out (Scheme 6). First, it was observed that the reaction was hardly inhibited in the presence of 2 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol



Scheme 6 Control experiments for mechanistic studies.

(BHT) as the radical inhibitor (Scheme 6a). This implied that the reaction might not proceed *via* a radical pathway. Moreover, the absence of TMSCN resulted in the generation of a stable product (**8**) in 42% yield and a trace amount of an unstable product (**11**), which could be detected by LC-MS (Scheme 6b). To prove the reaction intermediate, the reaction between **8** and TMSCN was performed with or without 2 equiv. of S_8 under standard conditions (Scheme 6c). Notably, only the reaction in the presence of S_8 could give **2a** in 96% yield. This result revealed that **8** is an important intermediate, which could react with S_8 and TMSCN to produce the final product through an unclear pathway.

On the basis of the results above and previous reports, a plausible mechanism was proposed (Scheme 7). Initially, a C–S bond is formed by a nucleophilic attack of an arene or heteroarene (**1**, **3** or **5**) on the S_8 ring, generating an intermediate (**9**), which can be changed into thiophenol **10**.[15] Then the oxidative homocoupling of thiophenol by DMSO readily generates a disulphide, **11**, which can be attacked by various nucleophiles. Because both the (hetero)arene and TMSCN have good nucleophilicity, there are two possible pathways (paths a and b) for thiocyanation. In the absence of TMSCN, the attack of the (hetero)arene on disulphide can generate a symmetrical thioether, **8**.[16] Although the details remain unclear at present, **8** could be converted to the thiocyanation product (**2**, **4** or **6**) in the coexistence of S_8 and TMSCN (Scheme 7, path a). Moreover, disulphide could be also directly attacked by TMSCN, giving the thiocyanation product and **10** (Scheme 7, path b).[17]



Scheme 7 A plausible mechanism for C–H thiocyanation.

In summary, we have developed a regioselective oxidative C–H thiocyanation of (hetero)arenes with elemental sulfur and TMSCN. Moreover, the selenocyanation process was also realized by replacing sulfur with selenium. Compared to previous reports, this protocol is distinguished by (1) avoiding the use of any catalyst or additive, (2) the novel SCN/SeCN source, (3) the different reaction mechanism, and (4) gram-scale synthesis. The current research paves a way for the application of elemental sulfur/selenium and TMSCN as a unique thio/selenocyanation source in organic chemistry.

We are grateful to the National Natural Science Foundation of China (21502177), the Education Bureau of Anhui Province (KJ2017A080, gxyqZD2018037), the Scientific and Technological Breakthrough Plan of Henan Province (182102310903), and the Doctoral Research Foundation of Zhengzhou University of Light Industry (2014BSJJ032).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) A. Houmam, E. M. Hamed and A. W. J. Still, *J. Am. Chem. Soc.*, 2003, **125**, 7258; (*b*) A. Casini, J.-Y. Winum, J.-L. Montero, A. Scozzafava and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 837; (*c*) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev.*, 2007, **107**, 5133; (*d*) J. T. Jarrett, *J. Biol. Chem.*, 2015, **290**, 3972; (*e*) M. Feng, B. Tang, S. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200.

2 For reviews, see: (*a*) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. Andy Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291; (*b*) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (*c*) Z. Qiao and X. Jiang, *Org. Biomol. Chem.*, 2017, **15**, 1942; C–H trifluoromethylthiolation: (*d*) C. Chen, L. Chu and F. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 12454; (*e*) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782; (*f*) C. Xu, B. Ma and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9316; (*g*) S. Guo, X. Zhang and P. Tang, *Angew. Chem., Int. Ed.*, 2015, **54**, 4065; (*h*) H. Wu, Z. Xiao, J. Wu, Y. Guo, J.-C. Xiao, C. Liu and Q.-Y. Chen, *Angew. Chem., Int. Ed.*, 2015, **54**, 4070; (*i*) W. Xu, J. Ma, X.-A. Yuan, J. Dai, J. Xie and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 10357; C–H thiolation: (*j*) F.-L. Yang and S.-K. Tian, *Angew. Chem., Int. Ed.*, 2013, **52**, 4929; (*k*) J. Yuan, X. Ma, H. Yi, C. Liu and A. Lei, *Chem. Commun.*, 2014, **50**, 14386; (*l*) Y. Yang, S. Zhang, L. Tang, Y. Hu, Z. Zha and Z. Wang, *Green Chem.*, 2016, **18**, 2609 C–H sulfonylation: (*m*) F. Xiao, H. Chen, H. Xie, S. Chen, L. Yang and G.-J. Deng, *Org. Lett.*, 2014, **16**, 50; (*n*) S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu and A. Lei, *Chem. Commun.*, 2014, **50**, 4496; (*o*) F. Xiao, S. Chen, Y. Chen, H. Huang and G.-J. Deng, *Chem. Commun.*, 2015, **51**, 652.

3 (*a*) R. Riemschneider, *J. Am. Chem. Soc.*, 1956, **78**, 844; (*b*) T. Nguyen, M. Rubinstein and C. Wakselman, *J. Org. Chem.*, 1981, **46**, 1938; (*c*) Z. Zhang and L. S. Liebeskind, *Org. Lett.*, 2006, **8**, 4331; (*d*) Y. T. Lee, S. Y. Choi and Y. K. Chung, *Tetrahedron Lett.*, 2007, **48**, 5673; (*e*) B. Exner, B. Bayarmagnai, F. Jia and L. J. Goossen, *Chem. – Eur. J.*, 2015, **21**, 17220; (*f*) B. Bayarmagnai, C. Matheis, K. Jouvin and L. J. Goossen, *Angew. Chem., Int. Ed.*, 2015, **54**, 5753.

4 (*a*) A. De Mico, R. Margarita, A. Mariani and G. Piancatelli, *Chem. Commun.*, 1997, 1237; (*b*) F. Wang, X. Yu, Z. Qi and X. Li, *Chem. – Eur. J.*, 2016, **22**, 511.

5 D. Yang, K. Yan, W. Wei, G. Li, S. Lu, C. Zhao, L. Tian and H. Wang, *J. Org. Chem.*, 2015, **80**, 11073.

6 G. Wu, Q. Liu, Y. Shen, W. Wu and L. Wu, *Tetrahedron Lett.*, 2005, **46**, 5831.

7 X.-Q. Pan, M.-Y. Lei, J.-P. Zou and W. Zhang, *Tetrahedron Lett.*, 2009, **50**, 347.

8 (*a*) V. K. Jadhav, R. R. Pal, P. P. Wadgaonkar and M. M. Salunkhe, *Synth. Commun.*, 2001, **31**, 3041; (*b*) J. S. Yadav, B. V. S. Reddy, S. Shubashree and K. Sadashiv, *Tetrahedron Lett.*, 2004, **45**, 2951; (*c*) M. A. Karimi Zarchi and R. Banihashemi, *J. Sulfur Chem.*, 2014, **35**, 458; (*d*) M. A. Karimi Zarchi and R. Banihashemi, *J. Sulfur Chem.*, 2016, **37**, 282.

9 (*a*) H. Jiang, W. Yu, X. Tang, J. Li and W. Wu, *J. Org. Chem.*, 2017, **82**, 9312; (*b*) J. Chen, T. Wang, T. Wang, A. Lin, H. Yao and J. Xu, *Org. Chem. Front.*, 2017, **4**, 130.

10 (*a*) W. Fan, Q. Yang, F. Xu and P. Li, *J. Org. Chem.*, 2014, **79**, 10588; (*b*) S. Mitra, M. Ghosh, S. Mishra and A. Hajra, *J. Org. Chem.*, 2015, **80**, 8275.

11 V. A. Kokorekin, V. L. Sigacheva and V. A. Petrosyan, *Tetrahedron Lett.*, 2014, **55**, 4306.

12 T. B. Nguyen, *Adv. Synth. Catal.*, 2017, **359**, 1066 and references therein.

13 (*a*) Y. Yan, Z. Li, H. Li, C. Cui, M. Shi and Y. Liu, *Org. Lett.*, 2017, **19**, 6228; (*b*) S.-S. Wu, C.-T. Feng, D. Hu, Y.-K. Huang, Z. Li, Z.-G. Luo and S.-T. Ma, *Org. Biomol. Chem.*, 2017, **15**, 1680; (*c*) Y. Yan, B. Niu, K. Xu, J. Yu, H. Zhi and Y. Liu, *Adv. Synth. Catal.*, 2016, **358**, 212; (*d*) Y. Yan, Y. Xu, B. Niu, H. Xie and Y. Liu, *J. Org. Chem.*, 2015, **80**, 5581.

14 (*a*) R. K. Das, S. K. U. Hossain and S. Bhattacharya, *Cancer Lett.*, 2005, **230**, 90; (*b*) J. Thomas, W. Maes, K. Robeyns, M. Ovaere, L. V. Meervelt, M. Smet and W. Dehaen, *Org. Lett.*, 2009, **11**, 3040; (*c*) N. B. Rashid Baig, R. N. Chandrakala, V. Sai Sudhir and S. Chandrasekaran, *J. Org. Chem.*, 2010, **75**, 2910; (*d*) J. C. Guillemin, *Curr. Org. Chem.*, 2011, **15**, 1670.

15 (*a*) T. B. Nguyen, L. Ermolenko, P. Retailleau and A. Al-Mourabit, *Angew. Chem., Int. Ed.*, 2014, **53**, 13808; (*b*) H. Xie, J. Cai, Z. Wang, H. Huang and G.-J. Deng, *Org. Lett.*, 2016, **18**, 2196.

16 (*a*) F. Shibahara, T. Kanai, E. Yamaguchi, A. Kamei, T. Yamauchi and T. Murai, *Chem. – Asian J.*, 2014, **9**, 237; (*b*) Y. Yang, W. Li, B. Ying, H. Liao, C. Shen and P. Zhang, *ChemCatChem*, 2016, **8**, 2916.

17 K. Yamaguchi, K. Sakagami, Y. Miyamoto, X. Jin and N. Mizuno, *Org. Biomol. Chem.*, 2014, **12**, 9200.

