RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 10258

Metal free C-3 chalcogenation (sulfenylation and selenylation) of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones†

Prasanjit Ghosh, Gautam Chhetri and Sajal Das *

Received 31st January 2021
Accepted 3rd March 2021

DOI: 10.1039/d1ra00834j

rsc.li/rsc-advances

An expeditious metal free C-3 chalcogenation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one has been devised to synthesize diversely orchestrated 3-ArS/ArSe derivatives in high yields (up to 95%). This operationally simple reaction proceeds under mild reaction conditions, can be executed in gram scale, and also highlights broad functional group tolerance. Preliminary experimental investigation suggests a radical mechanistic pathway for these transformations.

Organosulfur species and derivatives thereof, have garnered a prominent position in contemporary organic synthesis.[1] They also have widespread applications in pharmaceuticals, bioactive compounds and polymer materials.[2] In addition, carbon-selenium-carbon skeletons are high value core structures for their extensive use as therapeutically active agents, such as antioxidant, antihypertensive, antimicrobial, antibacterial, antiviral, anticancer agents *etc.*[3] Moreover, organoselenium species have been identified as non-toxic compounds.[4] Some of the biologically active C–S/C–Se linkage containing scaffolds is outlined in Fig. 1. Consequently, numerous efforts have been devoted to develop facile and reliable methods for the installation of a sulfenyl/selenyl group into organic frameworks.[5] Apart from the cross-coupling approach, an alternative protocol for the transition-metal-catalyzed C–S bond formation *via* C–H bond functionalization has been established, which is known as a sulfenylation reaction.[6] In this reaction, aryl sulfonyl hydrazides,[7] arylsulfonyl chlorides,[8] sulfinic acids,[9] and sodium sulfinates[10], thiols[11] are mostly used as the sulfenylating agents. Although, these methods are advantageous, certain limitations comprising the use of metal catalyst and toxic reagents still persist. Complete removal of trace amounts of transition-metal residues from the anticipated bioactive products is quite challenging task, and this contamination of a transition metal also inhibits the sustainable development.[12] Despite these accomplishments, development of an efficient and practical method for transition-metal-free C–S/Se bond forming reactions using thiols/diselenide as the sulfenylation/selenation reagent is an attractive and synthetically desirable.

On the other hand, *N*-fused bicyclic heterocycles[13] has received enormous interest from synthetic chemists as well as medicinal researchers due to their profound impact in agrochemicals, pharmaceuticals and material sciences.[14] In this family, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Fig. 1) exhibits versatile biological activities,[15] such as CXCR3 antagonism,[16] HLE inhibition,[17] MexAB-OprM specific efflux pump inhibition,[18] potent 5-HT6 antagonists,[19] and acetylcholinesterase inhibition.[20] Meanwhile, Pd catalyzed direct arylation and alkenylation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one through C–H bond functionalization has already been reported in the literature.[21] Rather, only a single report for the insertion of –SAr group in 4*H*-pyrido[1,2-*a*]pyrimidin-4-one molecule using sulfonyl hydrazides as thiol surrogates is documented by Wang *et al.*[22] Nevertheless, this protocol is effective at elevated temperature. Based on our research interests on the structural diversification of heterocyclic scaffolds, we recently reported different methodologies for the metal free direct C–H bond functionalization.[23] Herein, we envisaged to disclose a straightforward and efficient protocol of sulfenylation/selenylation for 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in the presence of iodine under mild conditions. Pleasingly, several thiols/organodiselenides are smoothly coupled with 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and furnished the desired anticipated products in good to excellent yields (Scheme 1).

We commenced our studies with the optimization of the sulfenylation reaction where 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1a**) and thiophenol were used as a model coupling partner

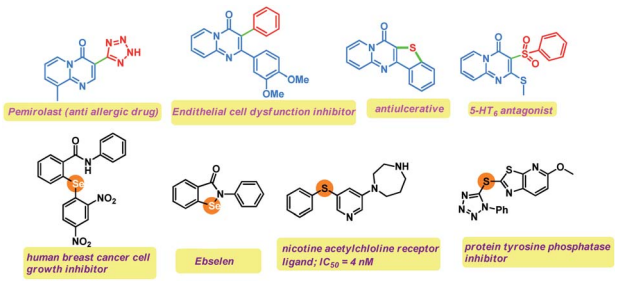
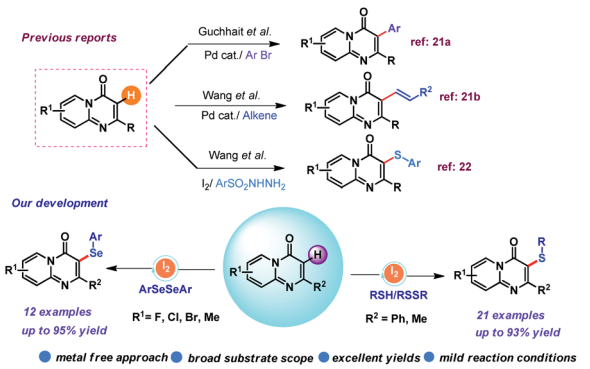


Fig. 1 Representative examples of some biologically active 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and diarylsulfide/diselenide scaffold.

Department of Chemistry, University of North Bengal, Darjeeling-734013, India. E-mail: sajal.das@hotmail.com; Fax: +91-0353-2699-001; Tel: +91-0353-2776-381

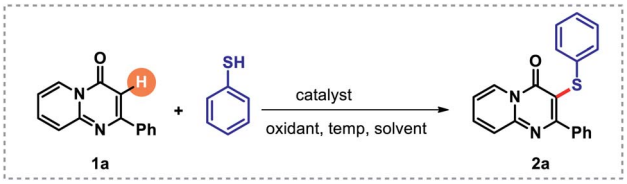
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra00834j



Scheme 1 Previous approaches and the present route of C–H bond functionalization of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

(Table 1). Initial attempts to couple them, using NaI and TBHP (as oxidant) in DMSO as a solvent at 100 °C remained unfruitful (Table 1, entry 1). No improvement was observed even after switching the solvent from DMSO to acetonitrile (Table 1; entry 2). However, yield of the expected product **2a** was raised to 50% upon using TBAI/$K_2S_2O_8$ in water (Table 1; entry 3). The reaction efficiency was further enhanced using one equiv. of TBAI in MeCN at 70 °C (Table 1; entry 4). Subsequently, several others inexpensive and readily available iodine/iodide additives were screened under aerobic condition (Table 1; entries 5–9). Delightedly, one equiv. of iodine provided the desired thiolated product **2a** in excellent (91%) yield at 70 °C (entry 5), after 12 h, while other forms of iodine additives were unable to promote this transformation effectively (Table 1; entries 6–9). It is noteworthy that except TBHP all others oxidant appears to be redundant in this reaction (Table 1; entries 10–13). Lowering the reaction temperature (50 °C and 30 °C) had a detrimental result on the reaction outcome (Table 1; entries 14–15). Notably, in absence of potassium persulfate, no desired product was detected in TLC, indicating that the oxidant has a decisive role for this sulfenylation reaction (Table 1; entry 16). Interestingly, consistent with our previous observation (Table 1; entry 5), using of 50 mol% of iodine also afforded the 92% yield of thiolated derivative **2a** (Table 1; entry 17). Other solvents were inefficient to provide decent yields (Table 1; entries 18–22). So it is evident from the optimization table that a combination of 50 mol% of iodine and $K_2S_2O_8$ (2 equiv.) as an oxidant in MeCN at 70 °C was found to be optimal for the sulfenylation reaction of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, which resulted in the formation of the corresponding 3-ArS derivative **2a** in excellent yield (92%) after 12 h (Table 1, entry 17).

Table 1 Screening of the reaction conditions: effect of reaction parameters[a]

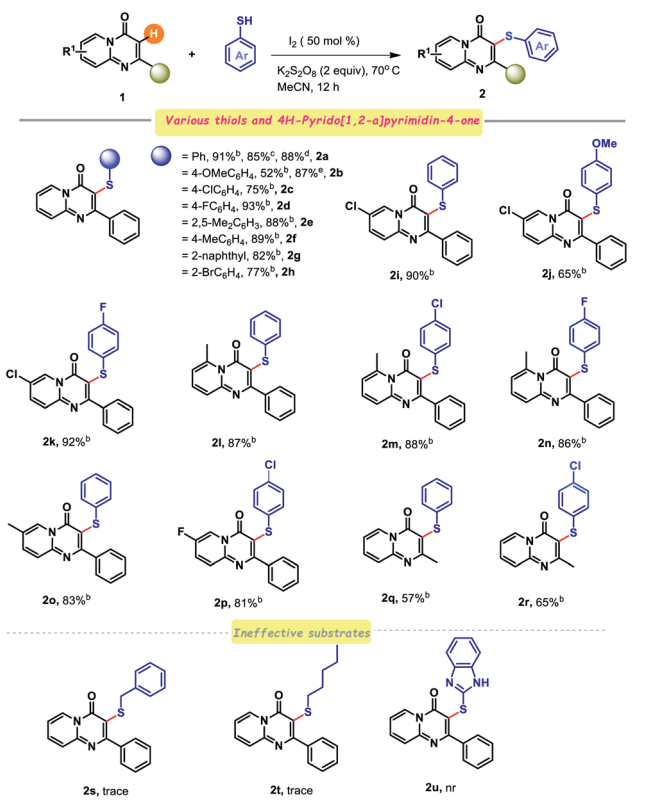


Entry	Reagent (equiv.)	Oxidant (equiv.)	Temperature (°C)	Solvent (ml)	Time (h)	Yield[b] (%)
1	NaI (3)	TBHP (3)	100	DMSO	24	NR
2	NaI (3)	TBHP (3)	100	CH_3CN	24	NR
3	TBAI (2)	$K_2S_2O_8$ (2)	70	H_2O	24	50
4	TBAI (1)	$K_2S_2O_8$ (2)	70	CH_3CN	12	67
5	I_2 (1)	$K_2S_2O_8$ (2)	70	CH_3CN	12	91
6	KI (1)	$K_2S_2O_8$ (2)	70	CH_3CN	12	NR
7	NaI (1)	$K_2S_2O_8$ (2)	70	CH_3CN	12	NR
8	NH_4I (1)	$K_2S_2O_8$ (2)	70	CH_3CN	12	60
9	NIS (1)	$K_2S_2O_8$ (2)	70	CH_3CN	12	63
10	I_2 (1)	TBHP (2)	70	CH_3CN	12	85
11	I_2 (1)	DTBP (2)	70	CH_3CN	12	NR
12	I_2 (1)	TBPB (2)	70	CH_3CN	12	NR
13	I_2 (1)	H_2O_2 (2)	70	CH_3CN	12	71
14	I_2 (1)	$K_2S_2O_8$ (2)	50	CH_3CN	12	53
15	I_2 (1)	$K_2S_2O_8$ (2)	30	CH_3CN	12	NR
16	I_2 (1)	—	70	CH_3CN	12	NR
17	**I_2 (50 mol%)**	**$K_2S_2O_8$ (2)**	**70**	**CH_3CN**	**12**	**92**
18	I_2 (50 mol%)	$K_2S_2O_8$ (2)	70	Toluene	12	35
19	I_2 (50 mol%)	$K_2S_2O_8$ (2)	70	Dioxane	12	41
20	I_2 (50 mol%)	$K_2S_2O_8$ (2)	70	DCE	12	66
21	I_2 (50 mol%)	$K_2S_2O_8$ (2)	70	EtOH	12	81
22	I_2 (50 mol%)	$K_2S_2O_8$ (2)	70	DMF	12	NR

[a] Reaction condition: 2-phenyl substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (0.125 mmol, 1 equiv.), benzene thiol (0.1875 mmol, 1.5 equiv.), inducer (equiv./mol%), solvent (2 ml), oxidant (3 equiv.). [b] Isolated yields based on the reactants **1a**, the reaction was run for 12–24 h.

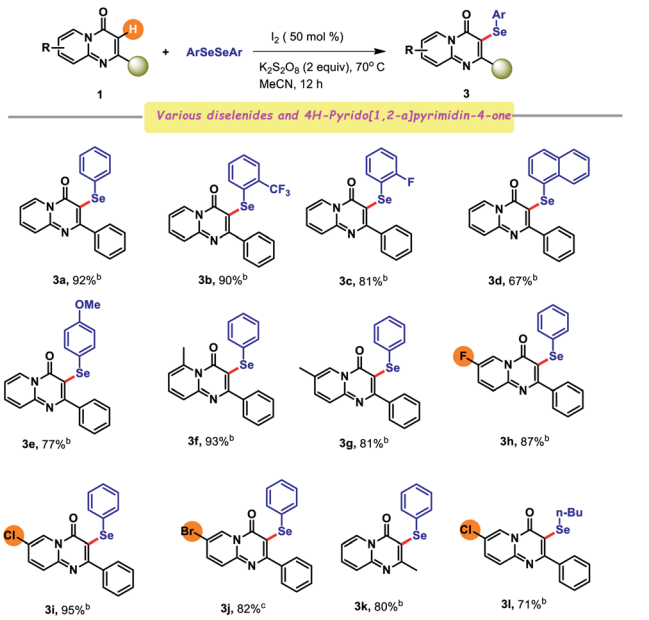
Having assimilated the robust reaction conditions for the C–S coupling of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, we sought to explore the scope and general applicability of this protocol (Table 2). A variety of 2-substituted-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was treated with a broad range of thiols, and the corresponding results are represented in Table 2. Satisfyingly, both electron-rich (–OMe, –Me) and electron-deficient (–F, –Cl, –Br) groups bearing benzene thiols reacted smoothly with 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, affording the desired 3-sulfenylated derivatives in good to excellent yields (Scheme 1; entries **2b–2h**). Noticeably, a crucial effect in the product yield was surveyed with the substituents present at the benzene thiol. 4-Methoxybenzene thiol furnished much lower yield of the corresponding coupled product (**2b**), compared to electron-withdrawing group, probably due to the generation of a more stable dimer [disulphide]. However, the yield of the anticipated product [**2b**] could further be enhanced upon/on using stoichiometric amount of catalyst (I_2). To our delight, maximum productivity of the product was obtained in the case of F-substituted benzenethiol compare to the other halogens. Notably, *ortho* bromo-substituted benzene thiol delivered in a higher yield of the corresponding product (**2h**) than the corresponding chloro derivative (**2c**). 2,5-Dimethylbenzene thiol was endured under the current reaction conditions to provide 88% yield of **2e**. Importantly, the bulkier naphthalene thiol also effectively participated in this transformation to give 82% yield of the C–S coupled product (**2g**). For adorning the synthetic potentiality further, we investigated the reactivity of various thiols with diverse 4*H*-pyrido[1,2-*a*]pyrimidin-4-one. Employment of both electron-neutral (–Me) and electron-deficient (–Cl) functional group substituted parent scaffold provided synthetically useful yields of the desired sulfenylated products with a wide spectrum of benzene thiols (entries **2i–2p**). In this context, a suitable choice of benzene thiols is also important, since electronic bias plays a pivotal role in this transformation (entries **2i–2p**). Comparatively, a higher yield of the desired ArS derivatives was always obtained in the presence of an electron-withdrawing group (–F, –Cl) at the *para* position of benzene thiol (entries **2k**, **2m**, **2n** and **2p**). Exposure of 2-alkyl substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-one with thiophenol and 4-chlorothiophenol was also fruitful to give intended products in acceptable yields (entries **2q** and **2r**). Unfortunately, benzyl thiol, 1-pentane thiol and heterocyclic congener of thiol (2-mercapto benzimidazole) did not respond under the optimal reaction conditions (entries **2s**, **2t** and **2u**). Especially, upscale synthesis of **2a** was also achieved, illuminating potential capabilities to assemble specialized 3-ArS substituted 4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones. It was remarkable that PhSSPh was also amenable instead of PhSH with this catalytic system.

Table 2 Scope of different substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and thiol derivatives for I_2 mediated sulfenylation[a]

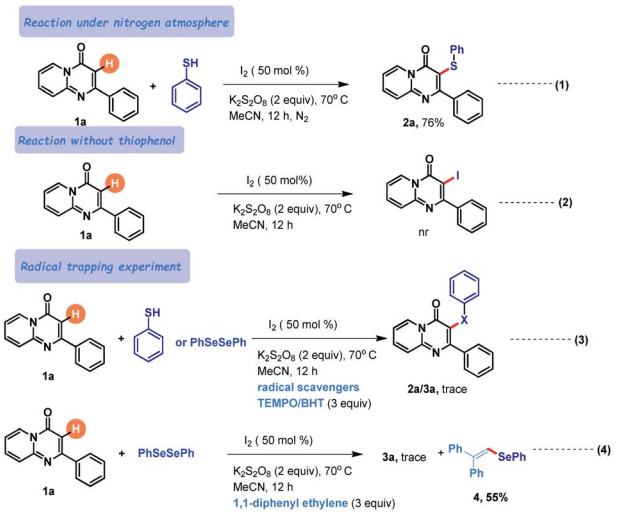


[a] Reaction condition: substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (0.125 mmol, 1 equiv.), thiol (0.1875 mmol, 1.5 equiv.), I_2 (50 mol%), MeCN (2 ml), $K_2S_2O_8$ (2 equiv.). [b] Isolated yields based on the reactants **1**, the reaction was run for 12 h. [c] Yield at 1 g scale. [d] PhSSPh was used instead of PhSH. [e] 1 equiv. of I_2 was used.

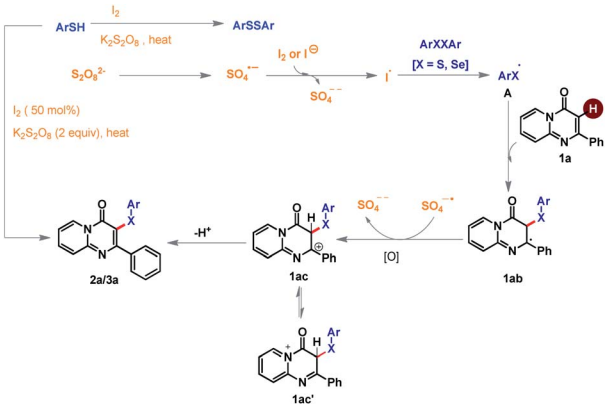
Table 3 Scope of different substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and diselenides derivatives for I_2 mediated selenylation[a]



[a] Reaction condition: various 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (0.125 mmol, 1 equiv.), organo diselenides (0.1875 mmol, 1.5 equiv.), I_2 (50 mol%), MeCN (2 ml), $K_2S_2O_8$ (2 equiv.). [b] Isolated yields based on the reactants **1**, the reaction was run for 12 h. [c] 1 equiv. of I_2 was used.



Scheme 2 Mechanistic studies.



Scheme 3 Plausible mechanism (radical pathway).

With the successful establishment of a straightforward and practical protocol for the C–S coupling reaction, we next investigated the broadness of the selenylation reaction between 2-substituted-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and organodiselenides for the selective installation of the –SeAr group at the C-3 position of parent precursor (Table 3). Generally, diphenyl diselenide was smoothly coupled with diverse functionalized 2-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, resulting in excellent yields of the final C–Se coupled products **3**. Various organo diselenides bearing electron-donating (–OMe) and electron-withdrawing groups (–CF_3 and –F) were found compatible, howbeit electron-deficient substrates showed better reactivity to render higher yields (entries **3b–3c**, **3e**). The methodology was successfully applied to bulkier naphthyl diselenide, delivering the desired product (**3d**) in 67% yield. Notably, halogen substituent (–F, –Br, –Cl) at the C-6 position of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one were tolerable, which are useful synthetic handle for late stage functionalization (entries **3h–3j**). Substrates having methyl functionality in the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one was also amenable (**3f–3g**) and smoothly produced the anticipated products in high yields (81−93%). Furthermore, reaction efficiency of C-2 alkyl substituted parent molecule was also evaluated, providing an excellent yield (80%) of the targeted 3-SeAr product **3k**. Besides to a broad range of aromatic diselenides, dibutyl diselenide also proved to be an efficient selenylating agent, offering the desired **3l** in 71% isolated yield.

To comprehend the plausible reaction mechanism, we executed the sulfenylation reaction under inert atmosphere (N_2) and isolated 76% yield of the desired product **2a** (Scheme 2; eqn (1)). This observation revealed that aerial oxygen was not only the sole oxidant for this transformation. Additionally, the reaction of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and iodine in presence potassium persulfate did not afford the corresponding iodo derivative (Scheme 2; eqn (2)). The result unambiguously confirmed that iodinated derivative of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one was not involved in the catalytic cycle. Furthermore, the presence of stoichiometric amount of radical scavengers (TEMPO, BHT and 1,1-diphenyl ethylene) inhibited the reactivity, refuting the involvement of non-radical pathway in the reaction mechanism (Scheme 2; eqn (3) and (4)). In addition, we have trapped the *in situ* generated radical intermediate (PhSe$^{\bullet}$) and isolated the compound **4** in reasonable yield (Scheme 2; eqn (4)).

On the basis of these findings and previous literature reports,[24] a plausible mechanistic pathway is elaborated in Scheme 3. Presumably, this sulfenylation/selenylation strategy involve an initial generation of the thiyl radical or selenyl radical species **A** ($^{\bullet}$SY/$^{\bullet}$SeY, Y = R) in presence of persulfate ($S_2O_8^{2-}$) or sulfate radical anion ($SO_4^{\bullet-}$). Subsequently, the reactive sulphur/selenyl radical intermediates **A** coupled with 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one substrate leading to a formation of next intermediate **1ab**. Then, it underwent further oxidation by sulfate radical anion *via* a SET mechanism to generate a cationic intermediate **1ac** which could be stabilized by resonance to **1ac′**. Lastly, the final coupled product (**2a**/**3a**) was formed with the liberation of H_2 species.

In summary, we have developed an efficient and straightforward transformative tool for regioselective chalcogenation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one under mild conditions. The protocol tolerated diverse common organic functional groups and resulted in good to excellent yields of the desired sulfenylated/selenylated products. Our methodology is operationally simple, regioselective, scalable and avoid the use any expensive metal catalyst. This present protocol opens a new avenue for the direct and convenient chalcogenation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one. Further, C–H bond functionalization reactions on 4*H*-pyrido[1,2-*a*]pyrimidin-4-one are currently underway in our laboratory and these observations will be forthcoming.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support (EMR/2016/001250) SERB, New Delhi is gratefully acknowledged. We also acknowledge DST-FIST for providing infrastructure facilities.

Notes and references

1 For selected examples: (*a*) C. B. Mishra, S. Kumari and M. Tiwari, *Eur. J. Med. Chem.*, 2015, **92**, 1; (*b*) A. Ayati, S. Emami, A. Asadipour, A. Shafiee and A. Foroumadi, *Eur. J. Med. Chem.*, 2015, **97**, 699; (*c*) P. Sun, D. Yang, W. Wei, L. Jiang, Y. Wang, T. Dai and H. Wang, *Org. Chem. Front.*, 2017, **4**, 1367; (*d*) M. Klečka, R. Pohl, J. Čejka and M. Hocek, *Org. Biomol. Chem.*, 2013, **11**, 5189.

2 For selected reviews and examples: (*a*) M. E. Peach, in *The Chemistry of the Thiol Group*, ed. S. Patai, John Wiley & Sons, London, 1979, pp. 721–756; (*b*) L. A. Damani, *Sulfur-Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology, Part B: Metabolism of Sulfur Functional Groups*, Ellis Horwood Ltd, Chichester, UK, 1989, vol. 1; (*c*) R. J. Cremlyn, in *An Introduction to Organosulfur Chemistry*, Wiley & Sons, New York, 1996; (*d*) M. D. McReynolds, J. M. Doughtery and P. R. Hanson, *Chem. Rev.*, 2004, **104**, 2239; (*e*) J. Zhao and X. Jiang, *Chin. Chem. Lett.*, 2018, **29**, 1079; (*f*) P. Chauhan, S. Mahajan and D. Enders, *Chem. Rev.*, 2014, **114**, 8807.

3 (*a*) D. A. Bellnier, D. N. Young, M. R. Detty, S. Camacho and A. R. Oseroff, *Photochem. Photobiol.*, 1999, **70**, 630; (*b*) K. A. Leonard, J. P. Hall, M. I. Nelen, S. R. Davies, S. O. Gollnick, S. Camacho, A. R. Oseroff, S. L. Gibson, R. Hilf and M. R. Detty, *J. Med. Chem.*, 2000, **43**, 4488.

4 (*a*) D. Kundu, S. Ahammed and B. C. Ranu, *Org. Lett.*, 2014, **16**, 1814; (*b*) S. Bhadra, A. Saha and B. C. Ranu, *J. Org. Chem.*, 2010, **75**, 4864; (*c*) R. J. Cohen, D. L. Fox and R. N. Salvatore, *J. Org. Chem.*, 2004, **69**, 4265.

5 (*a*) G. Li, Z. Gan, K. Kong, X. Dou and D. Yang, *Adv. Synth. Catal.*, 2019, **361**, 1808; (*b*) W. Wei, L. Wang, H. Yue, Y.-Y. Jiang and D. Yang, *Org. Biomol. Chem.*, 2018, **16**, 8379; (*c*) X. Wang, M. Yang, W. Xie, X. Fan and J. Wu, *Chem. Commun.*, 2019, **55**, 6010.

6 (*a*) K. Inamoto, C. Hasegawa and K. Hiroya, *Org. Lett.*, 2008, **10**, 5147; (*b*) L. L. Joyce and R. A. Batey, *Org. Lett.*, 2009, **11**, 2792; (*c*) C. Shen, H. Xia, H. Yan, X. Chen, S. Ranjit, X. Xie, D. Tan, R. Lee, Y. Yang, B. Xing, K. Huang, P. Zhang and X. Liu, *Chem. Sci.*, 2012, **3**, 2388; (*d*) R. Xu, J. P. Wan, H. Mao and Y. Pan, *J. Am. Chem. Soc.*, 2010, **132**, 15531; (*e*) J. Zhu, Z. Chen, H. Xie, S. Li and Y. Wu, *Org. Lett.*, 2010, **12**, 2434; (*f*) C. Xu and Q. Shen, *Org. Lett.*, 2014, **16**, 2046.

7 (*a*) A. K. Bagdi, S. Mitra, M. Ghosh and A. Hajra, *Org. Biomol. Chem.*, 2015, **13**, 3314; (*b*) X. Zhao, T. Li, L. Zhang and K. Lu, *Org. Biomol. Chem.*, 2016, **14**, 1131.

8 Q. Wu, D. Zhao, X. Qin, J. Lan and J. You, *Chem. Commun.*, 2011, **47**, 9188.

9 C.-R. Liu and L.-H. Ding, *Org. Biomol. Chem.*, 2015, **13**, 2251.

10 F. Xiao, S. Chen, J. Tian, H. Huang, Y. Liu and G.-J. Deng, *Green Chem.*, 2016, **18**, 1538.

11 Y. Liao, P. Jiang, S. Chen, H. Qi and G.-J. Deng, *Green Chem.*, 2013, **15**, 3302.

12 (*a*) D. Nair, J. Scarpello, L. White, L. M. Freitas dos Santos, I. Vankelecom and A. Livingston, *Tetrahedron Lett.*, 2001, **42**, 8219; (*b*) *The European Agency for the Evaluation of Medicinal Products; Committee for Proprietary Medicinal Products*; London, 2002; (*c*) J. Rivera-Utrilla, I. Bautista-Toledo, M. Ferro-Garcia and C. Moreno Castilla, *Carbon*, 2003, **41**, 323; (*d*) C. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889, For reviews on green chemistry, see: ; (*e*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998; (*f*) C.-J. Li and B. M. Trost, Green chemistry for chemical synthesis, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 13197; (*g*) P. J. Dunn, *Chem. Soc. Rev.*, 2012, **41**, 1452.

13 (*a*) A. K Bagdi, S. Santra, K. Monira and A. Hajra, *Chem. Commun.*, 2015, **51**, 1555; (*b*) A. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S. K. Guchhait, C. N. Kundu, U. C. Banerjee and P. V. Bharatam, *J. Med. Chem.*, 2011, **54**, 5013; (*c*) I. V. Seregin, A. W. Schammel and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 3433; (*d*) D. Chernyak, S. B. Gadamsetty and V. Gevorgyan, *Org. Lett.*, 2008, **10**, 2307; (*e*) O. R. Thiel, M. M. Achmatowicz, A. Reichelt and R. D. Larsen, *Angew. Chem., Int. Ed.*, 2010, **49**, 8395.

14 (*a*) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347; (*b*) L. D. Quin and J. A. Tyrell, *The Importance of Heterocycles in Medicine: Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*, John Wiley & Sons, Inc, Hoboken, NJ, 2010, p. 196.

15 (*a*) K. Nakayama, H. Kawato, J. Watanabe, M. Ohtsuka, K. Yoshida, Y. Yokomizo, A. Sakamoto, N. Kuru, T. Ohta, K. Hoshino, K. Yoshida, H. Ishida, A. Cho, M. H. Palme, J. Z. Zhang, V. J. Lee and W. J. Watkins, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 475; (*b*) K. Nakayama, N. Kuru, M. Ohtsuka, Y. Yokomizo, A. Sakamoto, H. Kawato, K. Yoshida, T. Ohta, K. Hoshino, K. Akimoto, J. Itoh, H. Ishida, A. Cho, M. H. Palme, J. Z. Zhang, V. J. Lee and W. J. Watkins, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2493; (*c*) G. Roma, N. Cinone, M. Di Braccio, G. Grossi, G. Leoncini, M. G. Signorello and A. Carotti, *Bioorg. Med. Chem.*, 2000, **8**, 751.

16 A.-R. Li, M. G. Johnson, J. Liu, X. Chen, X. Du, J. T. Mihalic, J. Deignan, D. J. Gustin, J. Duquette, Z. Fu, L. Zhu, A. P. Marcus, P. Bergeron, L. R. McGee, J. Danao, B. Lemon, T. Carabeo, T. Sullivan, J. Ma, L. Tang, G. Tonn, T. L. Collins and J. C. Medina, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 688.

17 M. Varga, Z. Kapui, S. Bátori, L. T. Nagy, L. Vasvári-Debreczy, E. Mikus, K. Urbán-Szabó and P. Arányi, *Eur. J. Med. Chem.*, 2003, **38**, 421.

18 K. Nakayama, Y. Ishida, M. Ohtsuka, H. Kawato, K. Yoshida, Y. Yokomiza, T. Ohta, K. Hoshino, T. Otani, Y. Kurosaka, K. Yoshida, H. Ishida, V. J. Lee, T. E. Renau and W. J. Watkins, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4205.

19 S. Hu, Y. Huang, Y.-J. Wu, H. He, K. A. Grant-Young, R. L. Bertekap, V. Whiterock, P. Brassil, K. Lentz, P. Sivaprakasam, D. R. Langley, R. S. Westphal and P. M. Scola, *Bioorg. Med. Chem.*, 2014, **22**, 1782.

20 C. T. Sadashiva, J. N. N. S. Chandra, K. C. Ponnappa, T. V. Gowda and K. S. Rangappa, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3932.

21 (*a*) S. K. Guchhait and G. Priyadarshani, *J. Org. Chem.*, 2015, **80**, 8482; (*b*) W. Liu, S. Wang, Q. Zhang, J. Yu, J. Li, Z. Xie and H. Cao, *Chem.–Asian J.*, 2014, **9**, 2436.

22 W. Liu, S. Wang, Z. Cai, Z. Li, J. Li and A. Wang, *Synlett*, 2018, **29**, 116.

23 (*a*) P. Ghosh, A. K. Nandi, G. Chhetri and S. Das, *J. Org. Chem.*, 2018, **83**, 12411; (*b*) P. Ghosh, G. Chhetri, A. K. Nandi, S. Sarkar, T. Saha and S. Das, *New J. Chem.*, 2019, **43**, 10959; (*c*) P. Ghosh, G. Chhetri, E. Perl and S. Das, *Adv. Synth. Catal.*, 2021, DOI: 10.1002/adsc.202001426.

24 (*a*) K. Phakdeeyothin and S. Yotphan, *Org. Biomol. Chem.*, 2019, **17**, 6432; (*b*) B. Hu, P. Zhou, Q. Zhang, Y. Wang, S. Zhao, L. Lu, S. Yan and F. Yu, *J. Org. Chem.*, 2018, **83**, 14978; (*c*) B. Hu, Q. Zhang, S. Zhao, Y. Wang, L. Xu, S. Yan and F. Yu, *Adv. Synth. Catal.*, 2019, **361**, 49; (*d*) Y. Liu, Y. Hu, Z. Cao, X. Zhan, W. Luo, Q. Liu and C. Guo, *Adv. Synth. Catal.*, 2019, **361**, 1084; (*e*) R. Semwal, C. Ravi, R. Kumar, R. Meena and S. Adimurthy, *J. Org. Chem.*, 2019, **84**, 792; (*f*) Y. Zheng, Y. He, G. Rong, X. Zhang, Y. Weng, K. Dong, X. Xu and J. Mao, *Org. Lett.*, 2015, **17**, 5444; (*g*) D. Yang, K. Yan, W. Wei, G. Li, S. Lu, C. Zhao, L. Tian and H. Wang, *J. Org. Chem.*, 2015, **80**, 11073.