OL | Organic Letters

pubs.acs.org/OrgLett

Letter

Preparation of Thiazole-2-thiones through TBPB-Promoted Oxidative Cascade Cyclization of Enaminones with Elemental Sulfur

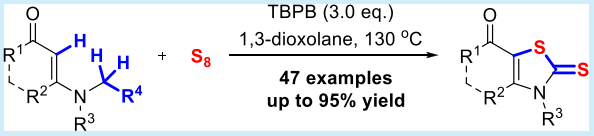
Biao Zhang, Donghan Liu, Yulin Sun, Yajing Zhang, Jiayi Feng, and Fuchao Yu*

Cite This: *Org. Lett.* 2021, 23, 3076–3082

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An unprecedented method for the construction of thiazole-2-thiones via an oxidative cascade cyclization strategy is described. The novel protocol involves the simultaneous formation of two C—S bonds and a C═S bond on the structure of enaminones in a single operation through a cascade of C(sp^2)—H/C(sp^3)—H bond sulfurations and C(sp^3)–H bond thiocarbonylation. This transformation allows for the efficient synthesis of thiazole-2-thiones with broad tolerance in moderate to excellent yields from simple enaminones with elemental sulfur.



Thiazoles belong to an important class of five-membered heterocyclic skeletons which ubiquitously occur in natural products,[1] bioactive molecules,[2] and functional materials,[3] as well as being widely used as synthetic intermediates in organic synthesis.[1a,4] Among them, thiazolone derivatives, especially thiazole-2-thiones, have widespread applications as valuable synthetic blocks that exhibit a variety of biological activities in drug discovery (Figure 1).[2a,5]

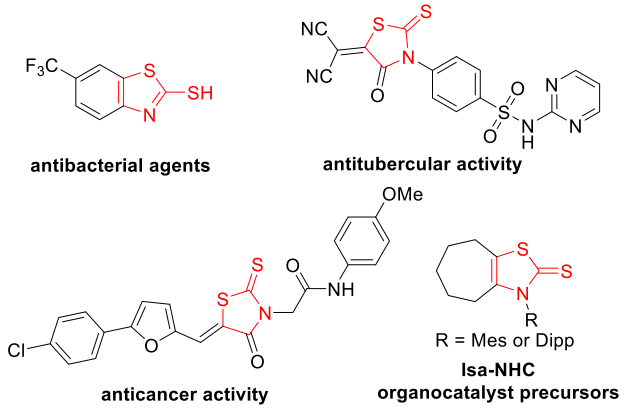


Figure 1. Selected examples of bioactive thiazole-2-thione molecules.

Furthermore, thiazole-2-thiones frequently serve as important synthetic precursors in organic synthesis (Figure 1).[6] Therefore, numerous synthetic methods have been developed toward the construction of structurally diverse thiazole-2-thiones.

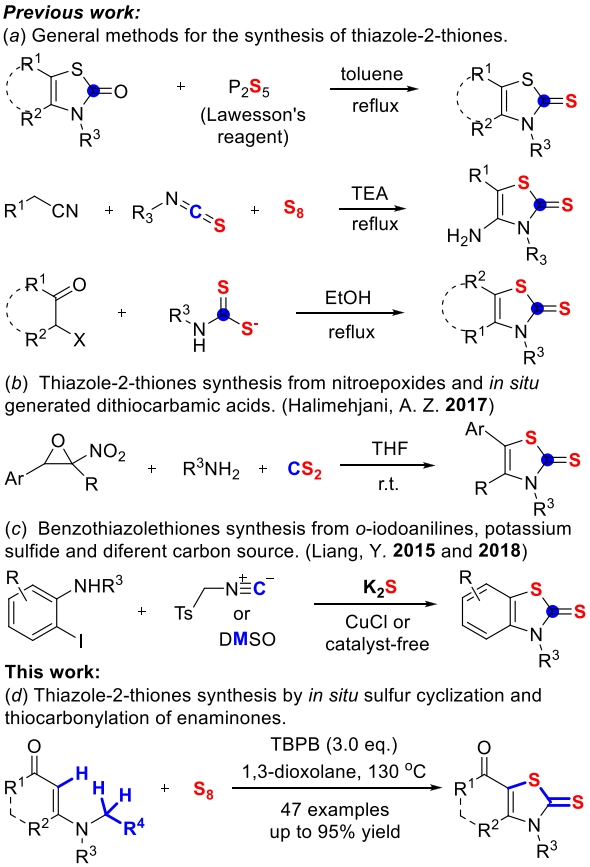
Among all of the synthetic approaches for thiazole-2-thiones, the vast majority of applications are accomplished through three conventional synthetic strategies (Scheme 1a): (1) thiocarbonylation of thiazole-2-ones via Lawesson's reagent;[5a,7] (2) cyclocondensation of isothiocyanates with cyanide compounds;[5b,8] and (3) cyclization of *o*-haloanilines with dithiocarbamate salts.[5d,e,9] Recently, Halimehjani and co-workers reported a facile and efficient method for the synthesis of thiazole-2(3*H*)-thiones from nitroepoxides and *in situ* generated dithiocarbamates in water (Scheme 1b).[10] Additionally, Liang and co-workers developed two elegant strategies for the synthesis of benzothiazolethiones through a three-component reaction of *o*-iodoanilines and K_2S with two different carbon sources in the presence or absence of CuCl, respectively (Scheme 1c).[11] However, most of these approaches suffer from some limitations, such as restricted starting materials, severe preparative limitations, harsh reaction conditions, and poor efficiencies, thereby restricting their utilities. Therefore, more efficient and practical methods for the synthesis of thiazole-2-thiones from simple and readily available starting materials are of great value.

New C—C/C—X bond formation via direct transformations of inert C—H bonds, especially C(sp^3)—H bonds with poorer acidity and higher bond energy, has emerged as a powerful strategy for the construction of valuable molecules.[12] On the other hand, enaminone chemistry has increasingly attracted the interest of synthetic chemists because of versatile reactive sites in their structures as building blocks for organic synthesis, which allows the construction of valuable heterocycles with structural diversity.[13] Direct transformations of C(sp^3)—H bonds in the enaminone structure have greatly enriched the diversity of enaminone-involved transformations. However, reports to describe the use of this strategy are scarce,[14] and this transformation involving the formation of

Received: March 4, 2021
Published: March 26, 2021

https://doi.org/10.1021/acs.orglett.1c00751
Org. Lett. 2021, 23, 3076–3082

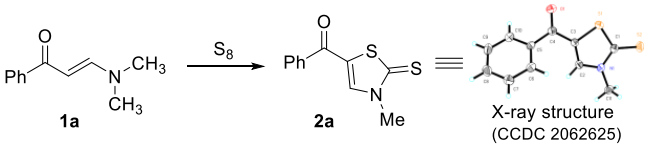
Scheme 1. Synthetic Methods of Thiazole-2-thiones



multiple new bonds in enaminones still remains with considerable challenges that lie ahead. For example, C-(sp^3)—H bonds on the aliphatic amine group in the enaminone structure could be achieved by this transformation to construct heterocycles, through inserting a heteroatom into the higher-electron-density double bonds of the α-carbon.[14a−d] With our continued interest in enaminone chemistry and direct transformations of C(sp^3)—H bonds,[15] herein, we first report a new approach for the construction of thiazole-2-thiones through *tert*-butyl peroxybenzoate (TBPB)-promoted oxidative cascade cyclization of enaminones with elemental sulfur. In this transformation, two C—S bonds and a C═S bond are efficiently formed via a sequenced C(sp^2)—H/C(sp^3)—H bond sulfuration, cyclization, and C(sp^3)—H thiocarbonylation process under metal-free conditions.

We started our investigation by choosing enaminones **1a** and elemental sulfur as model substrates. To our delight, the desired thiazole-2-thione **2a** was obtained in 83% yield in the presence of dicumyl peroxide (DCP) with 4.0 equiv in 1,3-dioxolane at 130 °C for 12 h (Table 1, entry 1), and its structure was unambiguously confirmed by X-ray crystallographic analysis (CCDC 2062625). Other solvents were screened, and it was revealed that 1,4-dioxane, acetonitrile, toluene, dimethyl sulfoxide (DMSO), and *N*,*N*-dimethylformamide (DMF) resulted in a lower yield than in 1,3-dioxolane (entries 2−6), while dichloromethane (DCM) and tetrahydrofuran (THF) gave unsuccessful results (entries 7 and 8). Next, a handful of oxidants were examined. *tert*-Butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), and cumyl hydroperoxide (CHP) proved to be ineffective for this cyclization reaction (entries 9−11). Dibenzoyl peroxide

Table 1. Optimization of Reaction Conditions[a,b]



entry	oxidant	solvent	T (°C)	time (h)	yield (%)
1	DCP (4 equiv)	1,3-dioxolane	130	12	83
2	DCP (4 equiv)	1,4-dioxane	130	12	55
3	DCP (4 equiv)	acetonitrile	130	12	52
4	DCP (4 equiv)	toluene	130	12	23
5	DCP (4 equiv)	DMSO	130	12	27
6	DCP (4 equiv)	DMF	130	12	36
7	DCP (4 equiv)	DCM	130	12	n.r.[c]
8	DCP (4 equiv)	THF	130	12	n.r.
9	TBHP (4 equiv)	1,3-dioxolane	130	12	n.r.
10	DTBP (4 equiv)	1,3-dioxolane	130	12	n.r.
11	CHP (4 equiv)	1,3-dioxolane	130	12	n.r.
12	BPO (4 equiv)	1,3-dioxolane	130	12	65
13	TBPB (4 equiv)	1,3-dioxolane	130	3	84
14	TBPB (4 equiv)	1,3-dioxolane	120	12	47
15	TBPB (4 equiv)	1,3-dioxolane	140	3	83
16	TBPB (2 equiv)	1,3-dioxolane	130	12	65
17	TBPB (3 equiv)	1,3-dioxolane	130	3	85
18	TBPB (5 equiv)	1,3-dioxolane	130	3	83

[a]Reaction conditions: **1a** (0.5 mmol), S_8 (1.5 mmol), oxidant in 2 mL of solvent. [b]Isolated yields. [c]n.r.: no reaction.

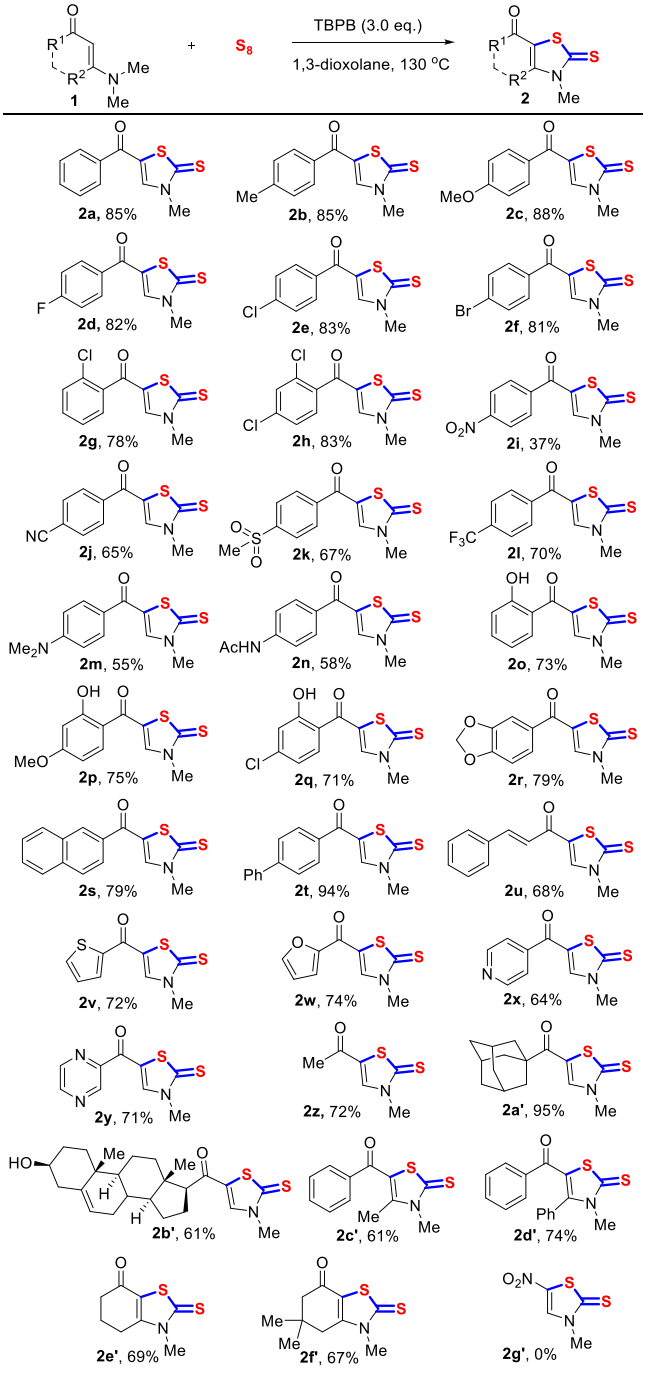
(BPO) afforded a low yield (entry 12). Gratifyingly, *tert*-butyl peroxybenzoate (TBPB) resulted in a sharp decrease of the reaction time, but the yield of **2a** was not affected (entry 13). When the reaction temperature was decreased to 120 °C, a significant reduction in the yield of product **2a** was observed (entry 14). Increasing the reaction temperature did not lead to any improvement (entry 15). Additionally, the effect of different oxidant loading was investigated, with 3.0 equiv found to give the best result in 85% yield (entries 16−18).

Under the optimized reaction conditions (Table 1, entry 17), various enaminone derivatives were investigated to expand the substrate scope of the TBPB-mediated cascade cyclization, and all results are summarized in Schemes 2−4.

Generally, when enaminones bearing *N*,*N*-dimethyl were examined in this transformation, the desired thiazole-2-thione products were obtained in satisfying yields (Scheme 2). A series of *N*,*N*-dimethyl enaminones containing either electron-donating (EDG) or electron-withdrawing (EWG) groups or halogen on the phenyl rings were well-tolerated, (**2a**−**2q**), though the nitro group afforded the desired product **2i** in slightly lower yield. Notably, the phenyl ring bearing free hydrogen groups, such as OH and AcNH, also successfully resulted in good reactivity and gave the desired products in 58−75% yields (**2n**−**2q**). Furthermore, enaminones with sterically hindered polycyclic and conjugated moieties, such as 2-naphthyl, 4-biphenyl, and styryl, were also compatible with this transformation, providing the corresponding products **2r**−**2u** in good to excellent yields. Satisfactorily, enaminones with heteroarene moieties, such as 2-thienyl, 2-furyl, 4-pyridyl, and 2-pyrazinyl, did not have an adverse effect on the reaction (**2v**−**2y**). To our delight, aliphatic enaminones, including methyl and 1-adamantyl, were successfully converted to the desired products **2z**−**2a′** in excellent yield. Importantly, to further explore the potential applicability of this method to the

https://doi.org/10.1021/acs.orglett.1c00751
Org. Lett. 2021, 23, 3076−3082

Scheme 2. Substrate Scope of *N,N*-Dimethyl Enaminones[a,b]

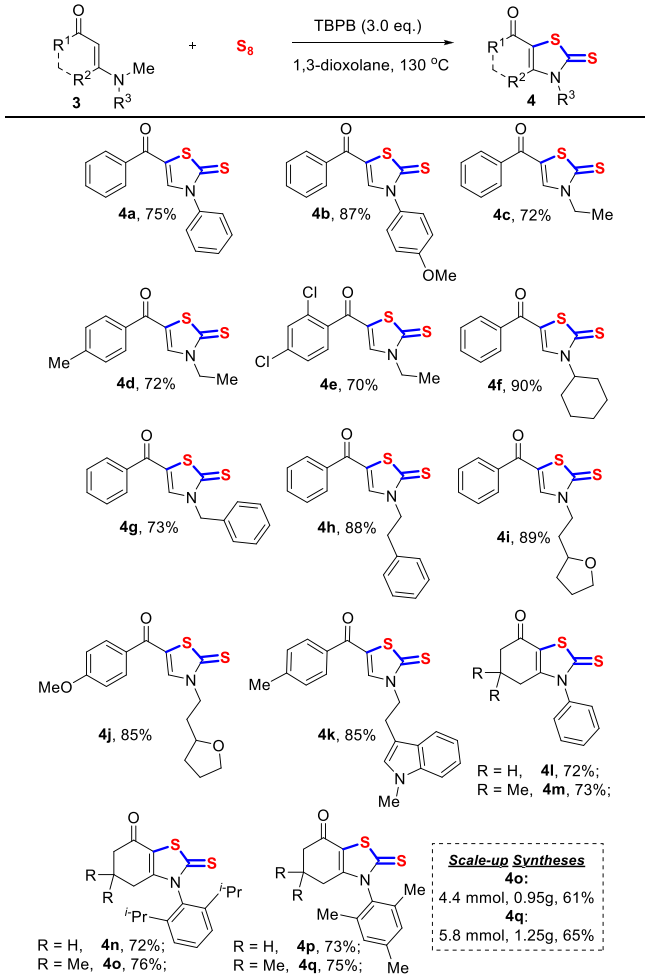


[a]Reaction conditions: **1** (0.5 mmol), S_8 (1.5 mmol), and TBPB (3.0 equiv) in 2 mL of 1,3-dioxolane, stirred at 130 °C for 3.0 h. [b]Isolated yields.

late-stage modification of complex molecules, we prepared a natural product-derived pregnenolone **1b′**, which reacted with elemental sulfur under the standard conditions to obtain the pregnenolone derivative **2b′** in moderate yield. Next, we examined the effect at the *β*-position substituents of enaminones in this transformation, affording the desired thiazole-2-thione products **2c′** and **2d′** in good yields, separately. Finally, the cascade cyclization of cyclic enaminones were carried out identically well to give the corresponding cyclic thiazole-2-thiones products **2e′** and **2f′** in moderate yields. However, with the nitro instead of the ketone of enaminones, the corresponding target product **2g′** was not observed.

After successful investigation of *N,N*-dimethyl enaminones, we wish to examine the utility of enaminones containing a wide variety of amine groups in our protocol (Schemes 3 and 4).

Scheme 3. Substrate Scope of *N*-Methyl-*N*-substituent Enaminones[a,b]



[a]Reaction conditions: **3** (0.5 mmol), S_8 (1.5 mmol), and TBPB (3.0 equiv) in 2 mL of 1,3-dioxolane, stirred at 130 °C for 3.0 h. [b]Isolated yields.

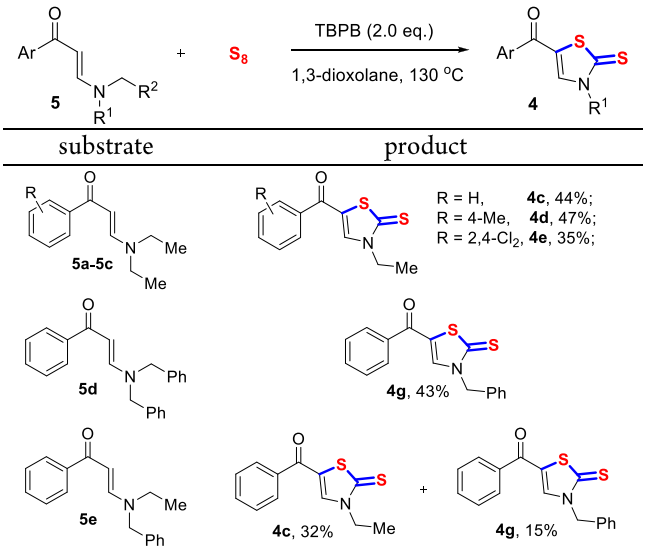
Accordingly, the scope and limitations of enaminones bearing an *N*-methyl group were evaluated (Scheme 3). Similar to the above-mentioned cascade cyclization reaction, both the *N*-aryl and *N*-alkyl group on the amine moiety were well-tolerated under optimal reaction conditions, affording the desired products (**4a**−**4k**) in good to excellent yields. Notably, when the amine moieties were all *N*-alkyl groups, including two $C(sp^3)$−H bond sulfuration reaction sites, this transformation was regioselectively carried out on the *N*-methyl group, due to the lower $C(sp^3)$−H bond strength of *N*-methyl than the $C(sp^3)$−$C(sp^3)$ bond of another *N*-alkyl group in the final thiocarbonylation process. Moreover, the *N*-aryl groups on cyclic enaminones were well-tolerated, giving the corresponding cyclic thiazole-2-thiones products (**4l**−**4q**) in moderate yields. To establish the feasibility of this approach for practical applications, scale-up reactions were then carried out,

https://doi.org/10.1021/acs.orglett.1c00751
Org. Lett. 2021, 23, 3076−3082

delivering the expected products **4o** (0.95 g) and **4q** (1.25 g) in 61% yield and 65% yield, respectively.

Considering the potential for the selective cleavage of two C(sp^3)−C(sp^3) bonds in the final thiocarbonylation process of enaminones bearing two *N*-alkyl groups, we next turned our attention to the compatibility and competitiveness of this transformation (Scheme 4). To our delight, enaminones

Scheme 4. Substrate Scope of *N,N*-Disubstituent Enaminones[a,b]

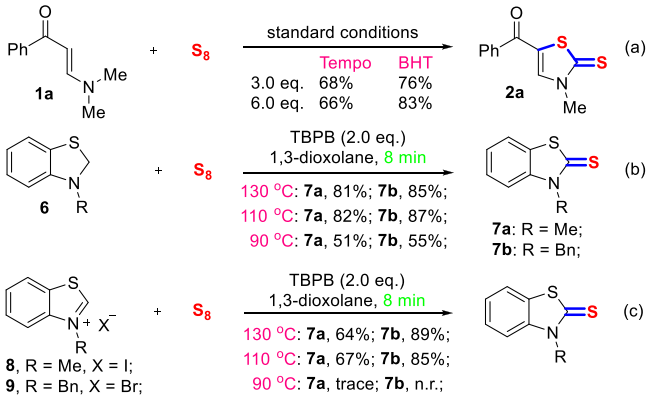


[a]Reaction conditions: **5** (0.5 mmol), S_8 (1.5 mmol), and TBPB (3.0 equiv) in 2 mL of 1,3-dioxolane, stirred at 130 °C for 3.0 h. [b]Isolated yields.

bearing two *N*-ethyl or *N*-benzyl groups participated in this cascade cyclization smoothly to provide the desired products (**4c**−**4e** and **4g**). Interestingly, this cascade cyclization reaction achieving on *N*-ethyl was superior to that with the *N*-benzyl group, when the amine moiety of enaminones **5e** were *N*-ethyl and *N*-benzyl, providing **4c** and **4g** in 32% and 15% yields, respectively. It should be stated that the relatively low yields of these desired products were mainly due to the need for the cleavage of the C(sp^3)−C(sp^3) bond on the *N*-alkyl group during the transformation. In addition, the reaction of elemental sulfur with in situ prepared enamines or enaminones was also investigated, but the corresponding target products were not observed (see the Supporting Information).

To elucidate the reaction mechanism of this cascade cyclization reaction, a series of control experiments were performed, as shown in Scheme 5. When 3.0 or 6.0 equiv of the radical inhibitors 2,2,6,6-tetramethylpiperidin1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added under the standard conditions, the reaction was almost unaffected (Scheme 5a). These results ruled out the possibility that this transformation was unlikely to involve a radical pathway. Subsequently, the thiocarbonylation of *N*-substituent 2,3-dihydrobenzo[*d*]thiazoles **6** with sulfur element under the optimal conditions in only 8 min afforded *N*-substituent benzo[*d*]thiazole-2(3*H*)-thione **7a** and **7b** in 81% yield and 85% yield, respectively. They could still proceed smoothly in 8 min when these reactions were carried out at 110 °C, but their yield decreased significantly at 90 °C (Scheme 5b). Unfortunately, this analogue could not be found in our

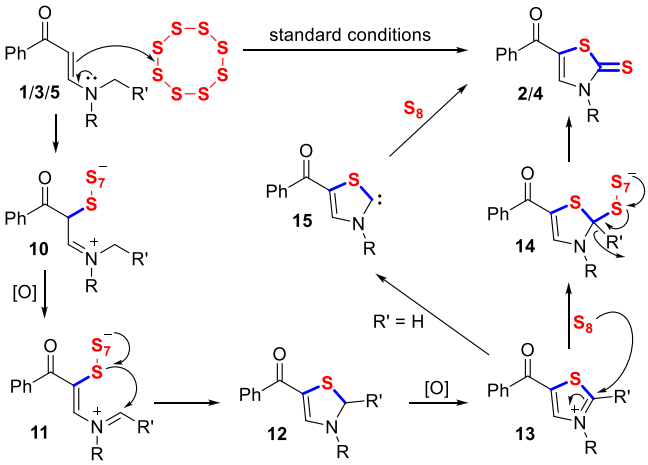
Scheme 5. Control Experiments



reaction system, which may not be stable because of the high reactivity of such intermediates. Furthermore, similar to the above-mentioned thiocarbonylation of *N*-substituent 2,3-dihydrobenzo[*d*]thiazoles, *N*-substituent benzo[d]thiazol-3-iums **8** and **9** worked well in 8 min at 130 and 110 °C, giving the expected products **7a** and **7b** in moderate to excellent yields (Scheme 5c). These results suggested that the thiocarbonylation process might not be a speed-determining step in the transformation, and the carbene intermediate might be formed in the thiocarbonylation process.

On the basis of the above-mentioned control experiments and previous studies of C(sp^3)−H bond transformation[14] and C−S bond formation[16] in enaminone chemistry, we proposed a plausible mechanism for this TBPB-promoted oxidative cascade cyclization (Scheme 6). Initially, sulfurated imine ion

Scheme 6. Possible Mechanism



species **10** was generated via the tautomerization of enaminones **1**/**3**/**5** and the nucleophilic attack of elemental sulfur (S_8), which undergo subsequent oxidation with oxidant to afford another imine ion species **11**.[17a,b] An intramolecular-cyclization on the *N*-alkyl group took place by the formation of a new C(sp^3)−S bond and delivered 4-thiazoline intermediate **12** with the release of sulfur (S_7). Thiazolinium intermediate **13** was produced after intermediate **12** proceeded in the second oxidation. Intermediate **13** proceeded in the second nucleophilic attack of S_8 and formed intermediate **14**. Finally, the desired products **2**/**4** would be obtained by the elimination of intermediate **14**. Furthermore, a simultaneous process

https://doi.org/10.1021/acs.orglett.1c00751
Org. Lett. 2021, 23, 3076−3082

promoted by thiazole carbenes **15** to generate the desired products **2**/**4** was also possible.[17c−e]

In summary, we have developed a novel TBPB-promoted oxidative cascade cyclization strategy for the efficient construction of thiazole-2-thione skeletons from enaminones and elemental sulfur in moderate to excellent yields. The protocol includes $C(sp^2)-H/C(sp^3)-H$ bond sulfuration of enaminones between the alkenyl and *N*-alkyl moieties, and the subsequent $C(sp^3)-H$ thiocarbonylation of the *N*-alkyl moieties, allowing for ready access to thiazole-2-thiones with a broad scope. Further efforts on the synthetic application of this strategy are ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00751.

Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2062625 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Fuchao Yu − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*; orcid.org/0000-0001-5557-3824; Email: yufc@kust.edu.cn

Authors

Biao Zhang − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Donghan Liu − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Yulin Sun − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Yajing Zhang − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Jiayi Feng − *Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00751

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21961018), the Natural Science Foundation of Yunnan Province (201901T070302), and the Plan of Funding Outstanding Young Talents of Yunnan Province.

■ REFERENCES

(1) (a) Gaumont, A.-C.; Gulea, M.; Levillain, J. Overview of the chemistry of 2-thiazolines. *Chem. Rev.* **2009**, *109*, 1371−1401. (b) Zhong, J. Muscarine, imidazole, oxazole and thiazole alkaloids. *Nat. Prod. Rep.* **2016**, *33*, 1268−1317. (c) Shaaban, K. A.; Shaaban, M.; Rahman, H.; Grün-Wollny, I.; Kämpfer, P.; Kelter, G.; Fiebig, H.-H.; Laatsch, H.; Karamomycins, A.-C. 2-naphthalen-2-yl-thiazoles from nonomuraea endophytica. *J. Nat. Prod.* **2019**, *82* (4), 870−877. (d) Wang, N.; Saidhareddy, P.; Jiang, X. Construction of sulfur-containing moieties in the total synthesis of natural products. *Nat. Prod. Rep.* **2020**, *37*, 246−275.

(2) (a) Jain, A. K.; Vaidya, A.; Ravichandran, V.; Kashaw, S. K.; Agrawal, R. K. Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorg. Med. Chem.* **2012**, *20*, 3378−3395. (b) Kumar, Y.; Green, R.; Wise, D. S.; Worting, L. L.; Townsend, L. B. Synthesis of 2,4-disubstituted thiazoles and selenazoles as potential antifilarial and antitumor agents. 2. 2-Arylamido and 2-alkylamido derivatives of 2-amino-4-(isothiocyanatomethyl)thiazole and 2-amino-4-(isothiocyanatomethyl) selenazole. *J. Med. Chem.* **1993**, *36*, 3849−3852. (c) Rouf, A.; Tanyeli, C. Bioactive thiazole and benzothiazole derivatives. *Eur. J. Med. Chem.* **2015**, *97*, 911−927. (d) Bursavich, M. G.; Harrison, B. A.; Blain, J.-F. Gamma secretase modulators: New alzheimer's drugs on the horizon? *J. Med. Chem.* **2016**, *59*, 7389−7409. (e) Cascioferro, S.; Parrino, B.; Carbone, D.; Schillaci, D.; Giovannetti, E.; Cirrincione, G.; Diana, P. Thiazoles, their benzofused systems, and thiazolidinone derivatives: Versatile and promising tools to combat antibiotic resistance. *J. Med. Chem.* **2020**, *63* (15), 7923−7956.

(3) (a) Hupfer, M. L.; Kaufmann, M.; Roussille, L.; Preiß, J.; Weiß, D.; Hinrichs, K.; Deckert, V.; Dietzek, B.; Beckert, R.; Presselt, M. Arylic versus alkylic-hydrophobic linkers determine the supramolecular structure and optoelectronic properties of tripodal amphiphilic push-pull thiazoles. *Langmuir* **2019**, *35*, 2561−2570. (b) Hupfer, M. L.; Kaufmann, M.; Herrmann-Westendorf, F.; Sachse, T.; Roussille, L.; Feller, K.-H.; Weiß, D.; Deckert, V.; Beckert, R.; Dietzek, B.; Presselt, M. On the ccontrol of chromophore orientation, supramolecular structure, and thermodynamic stability of an amphiphilic pyridyl-thiazol upon lateral compression and spacer length variation. *ACS Appl. Mater. Interfaces* **2017**, *9*, 44181−44191. (c) Singh, Y.; Stoermer, M. J.; Lucke, A. J.; Guthrie, T.; Fairlie, D. P. Structural mimicry of two cytochrome b(562) interhelical loops using macrocycles constrained by oxazoles and thiazoles. *J. Am. Chem. Soc.* **2005**, *127* (18), 6563−6572. (d) Murai, T.; Hori, F.; Maruyama, T. Intramolecular cyclization of in situ generated adducts formed between thioamide dianions and thioformamides leading to generation of 5-amino-2-thiazolines and 5-aminothiazoles, and their fluorescence properties. *Org. Lett.* **2011**, *13*, 1718−1721. (e) Ando, S.; Murakami, R.; Nishida, J.; Tada, H.; Inoue, Y.; Tokito, S.; Yamashita, Y. High performance *n*-type organic field-effect transistors based on pi-electronic systems with trifluoromethylphenyl groups. *J. Am. Chem. Soc.* **2005**, *127*, 5336−5337.

(4) (a) Huang, A.; Guo, X.; Li, P.; Li, W. Recent advances in catalytic asymmetric reactions of thiazolones, rhodanines and their derivatives. *Adv. Synth. Catal.* **2020**, *362*, 3542−3557. (b) Song, Y.-X.; Du, D.-M. Recent advances in the catalytic asymmetric reactions of thiazolone derivatives. *Org. Biomol. Chem.* **2020**, *18*, 6018−6041. (c) Gaumont, A.-C.; Gulea, M.; Levillain, J. Overview of the chemistry of 2-thiazolines. *Chem. Rev.* **2009**, *109*, 1371−1401. (d) Zhang, H.-J.; Lin, W.; Wu, Z.; Ruan, W.; Wen, T.-B. Silver-mediated direct phosphorylation of benzothiazoles and thiazoles with diarylphosphine oxides. *Chem. Commun.* **2015**, *51*, 3450−3453. (e) Liu, W.; Yu, X.; Kuang, C. Palladium-catalyzed C-2 selective olefination of thiazoles. *Org. Lett.* **2014**, *16*, 1798−1801.

(5) (a) Mésangeau, C.; Narayanan, S.; Green, A. M.; Shaikh, J.; Kaushal, N.; Viard, E.; Xu, Y.-T.; Fishback, J. A.; Poupaert, J. H.; Matsumoto, R. R.; McCurdy, C. R. Conversion of a highly selective

sigma-1 receptor-ligand to sigma-2 receptor preferring ligands with anticocaine activity. *J. Med. Chem.* **2008**, *51*, 1482−1486. (b) El-Gaby, M. S.A.; El-Hag Ali, G. A. M.; El-Maghraby, A. A.; El-Rahman, M. T. A.; Helal, M. H. M. Synthesis, characterization and in vitro antimicrobial activity of novel 2-thioxo-4-thiazolidinones and 4,40-bis (2-thioxo-4-thiazolidinone-3-yl)diphenylsulfones. *Eur. J. Med. Chem.* **2009**, *44*, 4148−4152. (c) Chandrappa, S.; Kavitha, C. V.; Shahabuddin, M. S.; Vinaya, K.; Ananda Kumar, C. S.; Ranganatha, S. R.; Raghavan, S. C.; Rangappa, K. S. Synthesis of 2-(5-((5-(4-chlorophenyl)furan-2-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid derivatives and evaluation of their cytotoxicity and induction of apoptosis in human leukemia cells. *Bioorg. Med. Chem.* **2009**, *17*, 2576−2584. (d) Liu, Y.; Xie, Z.; Zhao, D.; Zhu, J.; Mao, F.; Tang, S.; Xu, H.; Luo, C.; Geng, M.; Huang, M.; Li, J. Development of the first generation of disulfide-based subtype selective and potent covalent pyruvate dehydrogenase kinase 1 (PDK1) inhibitors. *J. Med. Chem.* **2017**, *60*, 2227−2244. (e) Epple, R.; Cow, C.; Xie, Y.; Azimioara, M.; Russo, R.; Wang, X.; Wityak, J.; Karanewsky, D. S.; Tuntland, T.; Nguyên-Trân, V. T. B.; Ngo, C. C.; Huang, D.; Saez, E.; Spalding, T.; Gerken, A.; Iskandar, M.; Seidel, H. M.; Tian, S.-S. Novel bisaryl substituted thiazoles and oxazoles as highly potent and selective peroxisome proliferator-activated receptor delta agonists. *J. Med. Chem.* **2010**, *53*, 77−105.

(6) (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by *N*-heterocyclic carbenes. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Ji, D.-S.; Luo, Y.-C.; Hu, X.-Q.; Xu, P.-F. Enantioselective synthesis of spirorhodanine-pyran derivatives *via* organocatalytic [3 + 3] annulation reactions between pyrazolones and rhodanine-derived ketoesters. *Org. Lett.* **2020**, *22* (3), 1028−1033. (c) Thompson, M.; Woodbury, N. W. Fluorescent and photochemical properties of a single zinc finger conjugated to a fluorescent DNA-binding probe. *Biochemistry* **2000**, *39*, 4327−4338. (d) Begum, I.; Kalisch, T.; Schnakenburg, G.; Kelemen, Z.; Nyulászi, L.; Streubel, R. [4 + 2]-Cycloadditions of a thiazol-based tricyclic 1,4-diphosphinine and a new easy 1,4-diphosphinine protection deprotection strategy. *Dalton Trans* **2020**, *49*, 12776−12779. (e) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. A family of thiazolium salt derived *N*-heterocyclic carbenes (NHCs) for organocatalysis: Synthesis, investigation and application in cross-benzoin condensation. *Eur. J. Org. Chem.* **2011**, *2011*, 5475−5484. (f) Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Maseras, F.; Kleij, A. W. Stereoselective and versatile preparation of tri- and tetrasubstituted allylic amine scaffolds under mild conditions. *J. Am. Chem. Soc.* **2016**, *138*, 11970−11978. (g) Lebeuf, R.; Hirano, K.; Glorius, F. Palladium-catalyzed C-allylation of benzoins and an NHC-catalyzed three component coupling derived thereof: compatibility of NHC- and Pd-catalysts. *Org. Lett.* **2008**, *10*, 4243−4246.

(7) (a) Abdelazeem, A. H.; Khan, S. I.; White, S. W.; Sufka, K. J.; McCurdy, C. R. Design, synthesis and biological evaluation of bivalent benzoxazolone and benzothiazolone ligands as potential anti-inflammatory/analgesic agents. *Bioorg. Med. Chem.* **2015**, *23*, 3248−3259. (b) El-Kady, M.; Abbas, E. M. H.; Salem, M. S.; Kassem, A. F. M.; Abd El-Moez, S. I. Synthesis and antimicrobial evaluation of novel 1,3-thiazoles and unsymmetrical azines. *Res. Chem. Intermed.* **2016**, *42*, 3333−3349.

(8) (a) Azam, F.; Alkskas, I. A.; Ahmed, M. A. Synthesis of some urea and thiourea derivatives of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidine and their antagonistic effects on haloperidol-induced catalepsy and oxidative stress in mice. *Eur. J. Med. Chem.* **2009**, *44*, 3889−3897. (b) Refaat, H. M. Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 2949−2956.

(9) (a) Katritzky, A. R.; Bayyuk, S. Novel rearrangement of a 3-amino-1,3-thiazole-2-thione. *Heterocycles* **1985**, *23*, 3099−3106. (b) Thomson, C. G.; Beer, M. S.; Curtis, N. R.; Diggle, H. J.; Handford, E.; Kulagowski, J. J. Thiazoles and thiopyridines: novel series of high affinity h5HT$_7$ ligands. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 677−680. (c) Salehi, M.; Ostad, S. N.; Riazi, G. H.; Assadieskandar, A.; Cheraghi-Shavi, T.; Shafiee, A.; Amini, M. Synthesis, cytotoxic evaluation, and molecular docking study of 4,5-diaryl-thiazole-2-thione analogs of combretastatin A-4 as microtubule-binding agents. *Med. Chem. Res.* **2014**, *23*, 1465−1473. (d) Balti, M.; Miller, S. A.; Efrita, M. L.; Leadbeater, N. E. An approach to the synthesis of 4−aryl and 5−aryl substituted thiazole−2(3H)−thiones employing flow processing. *RSC Adv.* **2016**, *6*, 72165−72169. (e) Zhu, L.; Zhang, M. Ortho−selective nucleophilic aromatic substitution reactions of polyhaloanilines with potassium/sodium *o*−ethyl xanthate: A convenient access to halogenated 2(3*H*)−benzothiazolethiones. *J. Org. Chem.* **2004**, *69*, 7371−7374.

(10) Ziyaei Halimehjani, A.; Lotfi Nosood, Y. Synthesis of *N,S*-heterocycles and dithiocarbamates by the reaction of dithiocarbamic acids and *S*-alkyl dithiocarbamates with nitroepoxides. *Org. Lett.* **2017**, *19*, 6748−6751.

(11) (a) Dang, P.; Zeng, W.; Liang, Y. Copper−catalyzed three−component synthesis of benzothiazolethiones from *o*-iodoanilines, isocyanide, and potassium sulfide. *Org. Lett.* **2015**, *17*, 34−37. (b) Zhu, X.; Li, W.; Luo, X.; Deng, G.; Liang, Y.; Liu, J. A catalyst−free and additive−free method for the synthesis of benzothiazolethiones from *o*−iodoanilines, DMSO and potassium sulfide. *Green Chem.* **2018**, *20*, 1970−1974.

(12) (a) Wang, M.; Huan, L.; Zhu, C. Cyanohydrin−mediated cyanation of remote unactivated C(sp^3)−H bonds. *Org. Lett.* **2019**, *21*, 821−825. (b) Qiu, Y.; Hartwig, J. F. Mechanism of Ni−catalyzed oxidations of unactivated C(sp^3)−H bonds. *J. Am. Chem. Soc.* **2020**, *142*, 19239−19248. (c) Chu, X.−Q.; Ge, D.; Shen, Z.−L.; Loh, T.−P. Recent advances in radical−initiated C(sp^3)−H bond oxidative functionalization of alkyl nitriles. *ACS Catal.* **2018**, *8*, 258−271.

(13) (a) Jiang, B.; Wang, X.; Xu, H.−W.; Tu, M.−S.; Tu, S.−J.; Li, G. Highly selective domino multicyclizations for forming polycyclic fused acridines and azaheterocyclic skeletons. *Org. Lett.* **2013**, *15*, 1540−1543. (b) Yuan, Y.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. Direct oxidative coupling of enamines and electron−deficient amines: TBAI/TBHP−mediated synthesis of substituted diaminoalkenes under metal−free conditions. *Org. Lett.* **2014**, *16*, 5410−5413. (c) Gu, Z.−Y.; Cao, J.−J.; Wang, S.−Y.; Ji, S.−J. The involvement of the trisulfur radical anion in electron−catalyzed sulfur insertion reactions: facile synthesis of benzothiazine derivatives under transition metal−free conditions. *Chem. Sci.* **2016**, *7*, 4067−4072. (d) Zhang, H.; Shen, J.; Cheng, G.; Feng, Y.; Cui, X. One−Pot Synthesis of Benzo[b][1,4]oxazins via Intramolecular Trapping Iminoenol. *Org. Lett.* **2018**, *20*, 664−667. (e) Yang, L.; Wei, L.; Wan, J.-P. Redox neutral [4 + 2] benzannulation of dienals and tertiary enaminones for benzaldehyde synthesis. *Chem. Commun.* **2018**, *54*, 7475−7478. (f) Sun, J.; Sun, Q.−S.; Yan, C.−G. Efficient synthesis of novel cyclic fused−phenothiazines via domino cyclization of 2−(benzo[*b*][1,4]-thiazin−3−ylidene)acetate, aromatic aldehydes and cyclic 1,3−diketones. *Org. Chem. Front.* **2019**, *6*, 3555−3561. (g) Yu, Q.; Zhang, Y.; Wan, J.−P. Ambient and aerobic carbon−carbon bond cleavage toward α−ketoester synthesis by transition−metal−free photocatalysis. *Green Chem.* **2019**, *21*, 3436−3441. (h) Fu, L.; Xu, Z.; Wan, J.−P.; Liu, Y. The domino chromone annulation and a transient halogenation−mediated C−H alkenylation toward 3−vinyl chromones. *Org. Lett.* **2020**, *22*, 9518−9523. (i) Zhang, C.−H.; Huang, R.; Qing, X.; Lin, J.; Yan, S.−J. Cascade reaction of isatins with nitro−substituted enamines: highly selective synthesis of functionalized (Z)−3−(1−(arylamino)−2−oxoarylidene)indolin−2−ones. *Chem. Commun.* **2020**, *56*, 3488−3491. (j) Li, K.; Huang, R.; Chen, L.; Lv, Y.; Yan, S.−J. Cu(II)/Iodine(III) oxide dimerization of heterocyclic ketene aminals: Tandem TEMPO oxidation for the highly selective synthesis of functionalized 2*H*−pyrrolo[1,2−*a*]-imidazol−7(3*H*)−ones. *Org. Lett.* **2020**, *22*, 8210−8214. (k) Zhou, S.; Liu, D.−Y.; Wang, S.; Tian, J.−S.; Loh, T.−P. An efficient method for the synthesis of 2−pyridones via C−H bond functionalization. *Chem. Commun.* **2020**, *56*, 15020−15023.

(14) (a) Wu, M.; Jiang, Y.; An, Z.; Qi, Z.; Yan, R. Iron−catalyzed synthesis of substituted thiazoles from enamines and elemental sulfur through C−S bond formation. *Adv. Synth. Catal.* **2018**, *360*, 4236−4240. (b) Ma, H.; Zhang, X.; Chen, L.; Yu, W. A domino azidation/

https://doi.org/10.1021/acs.orglett.1c00751
Org. Lett. 2021, 23, 3076−3082

C−H amination approach toward trifluoromethyl substituted imidazoles. *J. Org. Chem.* **2017**, *82*, 11841−11847. (c) Wu, P.; He, Y.; Wang, H.; Zhou, Y.−G.; Yu, Z. Copper(II)−catalyzed C−H nitrogenation/annulation cascade of ketene *N,S*-acetals with aryldiazonium salts: A direct access to N_2-substituted triazole and triazine derivatives. *Org. Lett.* **2020**, *22*, 310−315. (d) Weng, Y.; Lv, W.; Yu, J.; Ge, B.; Cheng, G. Preparation of 2,4,5−trisubstituted oxazoles through iodinemediated aerobic oxidative cyclization of enaminones. *Org. Lett.* **2018**, *20*, 1853−1856. (e) Huang, J.; Yu, F. Recent advances in organic synthesis based on N,N−dimethyl enaminones. *Synthesis* **2021**, *53*, 587. (f) Yu, F.; Zhou, B.; Xu, H.; Chang, K.−J.; Shen, Y. *Tetrahedron Lett.* **2015**, *56*, 837. (g) Zhao, M.−N.; Zhang, Z.−J.; Ren, Z.−H.; Yang, D.−S.; Guan, Z.−H. Copper−catalyzed oxidative cyclization/1,2−amino migration cascade reaction. *Org. Lett.* **2018**, *20*, 3088−3091.

(15) (a) Yu, F.; Yan, S.; Hu, L.; Wang, Y.; Lin, J. Cascade reaction of isatins with heterocyclic ketene aminals: synthesis of imidazopyrrolo−quinoline derivatives. *Org. Lett.* **2011**, *13*, 4782−4785. (b) Yu, F.; Huang, R.; Ni, H.; Fan, J.; Yan, S.; Lin, J. Novel three−component stereoselective synthesis of spirooxindole derivatives. *Green Chem.* **2013**, *15*, 453−462. (c) Xu, H.; Zhou, B.; Zhou, P.; Zhou, J.; Shen, Y.; Yu, F.; Lu, L. Insights into the unexpected chemoselectivity in brønsted acid catalyzed cyclization of isatins with enaminones: convenient synthesis of pyrrolo[3,4−c]quinolin−1−ones and spirooxindoles. *Chem. Commun.* **2016**, *52*, 8002−8005. (d) Zhou, P.; Hu, B.; Li, L.; Rao, K.; Yang, J.; Yu, F. $Mn(OAc)_3$−promoted oxidative Csp^3−P bond formation through Csp^2−Csp^2 and P−H bond cleavage: Access to *β*−ketophosphonates. *J. Org. Chem.* **2017**, *82*, 13268−13276. (e) Hu, B.; Zhang, Q.; Zhao, S.; Wang, Y.; Xu, L.; Yan, S.; Yu, F. Direct oxidative disulfenylation/cyclization of 2'−hydroxyacetophenones with thiophenols for the synthesis of 2,2−dithio−benzofuran−3(2*H*)−ones. *Adv. Synth. Catal.* **2019**, *361*, 49−54. (f) Hu, B.; Zhou, P.; Zhang, Q.; Wang, Y.; Zhao, S.; Lu, L.; Yan, S.; Yu, F. Metal−free oxidative thioesterification of methyl ketones with thiols/disulfides for the synthesis of *α*-ketothioesters. *J. Org. Chem.* **2018**, *83*, 14978−14986.

(16) (a) Fu, L.; Wan, J.-P. C_3-Functionalized chromones synthesis by tandem C-H elaboration and chromone annulation of enaminones. *Asian J. Org. Chem.* **2019**, *8*, 767−776. (b) Sun, J.; Zhang-Negrerie, D.; Du, Y. Oxidative coupling of enamines and disulfides *via* tetrabutylammonium iodide/tert-butyl hydroperoxide-mediated intermolecular oxidative C(sp^2)-S bond formation under transition metal-free conditions. *Adv. Synth. Catal.* **2016**, *358*, 2035−2040. (c) Siddaraju, Y.; Prabhu, K. R. Iodine-catalyzed cross dehydrogenative coupling reaction: sulfenylation of enaminones using dimethyl sulfoxide as an oxidant. *J. Org. Chem.* **2017**, *82*, 3084−3093. (d) Zhong, S.; Liu, Y.; Cao, X.; Wan, J.-P. KIO_3-Catalyzed domino C(sp^2)-H bond sulfenylation and C-N bond oxygenation of enaminones toward the synthesis of 3-sulfenylated chromones. *ChemCatChem* **2017**, *9*, 465−468. (e) Gao, Y.; Wei, L.; Liu, Y.; Wan, J.-P. Iodine-mediated synthesis of sulfur-bridged enaminones and chromones *via* double C(sp^2)−H thiolation. *Org. Biomol. Chem.* **2017**, *15*, 4631−4634. (f) Wan, J.-P.; Zhong, S.; Xie, L.; Cao, X.; Liu, Y.; Wei, L. KIO_3-Catalyzed aerobic cross-coupling reactions of enaminones and thiophenols: Synthesis of polyfunctionalized alkenes by metal-free C−H sulfenylation. *Org. Lett.* **2016**, *18*, 584−587.

(17) (a) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. CuI/BF_3·Et_2O Cocatalyzed aerobic dehydrogenative reactions of ketones with benzylamines: facile synthesis of substituted imidazoles. *Org. Lett.* **2012**, *14*, 6068−6071. (b) Wang, X.; Qiu, X.; Wei, J.; Liu, J.; Song, S.; Wang, W.; Jiao, N. Cu-Catalyzed aerobic oxidative sulfuration/annulation approach to thiazoles *via* multiple Csp^3−H bond cleavage. *Org. Lett.* **2018**, *20*, 2632−2636. (c) Nelson, D. J.; Nolan, S. P. Quantifying and understanding the electronic properties of *N*−heterocyclic carbenes. *Chem. Soc. Rev.* **2013**, *42*, 6723−6753. (d) Deng, J.−C.; Chen, J.−H.; Zhang, J.−R.; Lu, T.−T.; Tang, R.−Y. Sulfite−induced *N*−alkylation and thioketonization of azoles enable access to diverse azole thiones. *Adv. Synth. Catal.* **2018**, *360*, 4795−4806. (e) Deng, J.−C.; Gao, Y.−C.; Zhu, Z.; Xu, L.; Li, Z.−D.; Tang, R.−Y. Sulfite−promoted synthesis of *N*−difluoromethylthioureas *via* the reaction of azoles with bromodifluoroacetate and elemental sulfur. *Org. Lett.* **2019**, *21*, 545−548.

https://doi.org/10.1021/acs.orglett.1c00751
Org. Lett. 2021, 23, 3076−3082