

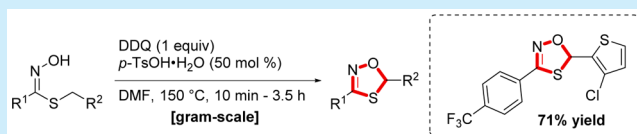
Synthesis of 1,4,2-Oxathiazoles via Oxidative Cyclization of Thiohydroxamic Acids

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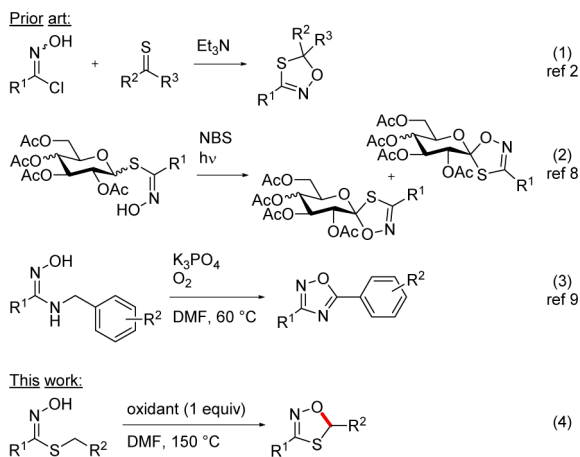
S Supporting Information

ABSTRACT: An oxidative formation of 1,4,2-oxathiazoles from readily available thiohydroxamic acids is reported. A variety of alkyl, aryl, and heteroaryl substituents are well tolerated for both the thiohydroxamic acid and activating fragments, and the reaction has been demonstrated on gram-scale. This reaction represents the only method currently available to prepare a diverse set of oxathiazoles and expands the chemistry of C–H oxidation via appended N–OH functional groups. Finally, we also demonstrate the rapid preparation of a 1,4,2-oxathiazole analog of an anticancer lead molecule.



Nitrogen containing heterocycles are prevalent in a majority of pharmaceutical compounds;¹ therefore, new ways to access existing and novel nitrogen heterocycles are always needed to expand the medicinal chemists' toolbox. 1,4,2-Oxathiazoles are 5-membered ring heterocycles containing three different heteroatoms that have been very scarcely reported in the literature.² Current approaches to their synthesis rely on [3 + 2] cycloaddition between a nitrile oxide and a thiocarbonyl (Scheme 1, eq 1), analogous to the

Scheme 1. Strategies for the Preparation of 1,4,2-Oxathiazoles



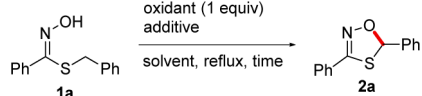
preparation of their oxygen and nitrogen counterparts.^{2,3} Due to the instability of thioaldehydes and thioketones, there are almost no 5-alkyl-1,4,2-oxathiazoles reported in the literature,⁴ yet these heterocycles could be of great utility for medicinal chemists as a new scaffold for SAR. Indeed, closely related heterocycles such as 1,2,4-oxadiazoles, thiazoles, and isoxazoles are privileged scaffolds for drug discovery.^{1,3,5} Moreover, 1,4,2-oxathiazoles have been shown to be useful isothiocyanate (ITC) precursors upon thermal decomposition.⁶ As part of our

efforts to investigate the use of thiohydroxamic acids as building blocks for synthesis,⁷ we discovered that they could be oxidized to access 5H-1,4,2-oxathiazoles (Scheme 1, eq 4). Prior work by Praly et al. reported the formation of 5,5'-spiroglucosyl-1,4,2-oxathiazoles via free-radical cyclization of S-glucosyl-thiohydroxamic acids (Scheme 1, eq 2).⁸ Chiba and co-workers described the oxidative cyclization of amidoximes via oxime radicals to afford 1,2,4-oxadiazoles (Scheme 1, eq 3).⁹ Despite these efforts, there remains no general method to access 1,4,2-oxathiazoles from readily available starting materials; therefore, we explored the oxidation of readily available thiohydroxamic acids to access 1,4,2-oxathiazoles.

Thiohydroxamic acid derivatives were easily prepared on scale in one step via alkylation of the corresponding thiohydroxamic acids^{7a} or in a two-step, one-pot process from the corresponding oximes via an improved procedure from our previously published method. Both methods provided a variety of thiohydroxamic acids from commercially available aldehydes. We began our optimization studies with the S-benzyl thiohydroxamic acid **1a** (Table 1).¹⁰ Upon heating at 100 °C in 1,4-dioxane with Cu^{II} as the oxidant, we obtained the desired 1,4,2-oxathiazole **2a** in 32% yield (entry 1) and confirmed its structure via X-ray analysis (see Figure S1). We then screened various solvents and temperatures, and the reaction yield was improved to 46% in DMF at 150 °C (entries 2–4). Employing Cu^I oxidants did not improve the yield of **2a** (Table S1); however, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided the desired product in 71% yield (entry 5). Solvents were screened again with DDQ (see Table S1) as the oxidant, and DMF remained the best solvent under anhydrous reaction conditions. In an effort to further optimize the process, we explored the use of additives. The addition of triethylamine decomposed the starting material (entry 6), while camphor-sulfonic acid (CSA) and pyridinium *p*-toluenesulfonate (PPTS)

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Table 1. Optimization of the Reaction Conditions^a

		
entry	conditions	2a (%) ^b
1	Cu(OAc) ₂ ·H ₂ O, 1,4-dioxane, 30 min	32
2	Cu(OAc) ₂ ·H ₂ O, toluene, 25 min	28
3	Cu(OAc) ₂ ·H ₂ O, DMSO, 15 min	34
4	Cu(OAc) ₂ ·H ₂ O, DMF, 20 min	46
5	DDQ, DMF, ^c 15 min	71
6	DDQ, DMF, ^c Et ₃ N (1 equiv), 10 min	^d
7	DDQ, DMF, ^c CSA (1 equiv), 1 h	71
8	DDQ, DMF, ^c PPTS (1 equiv), 15 min	71
9	DDQ, DMF, ^c <i>p</i> -TsOH·H ₂ O (1 equiv), 15 min	83
10	DDQ, DMF, ^c <i>p</i> -TsOH·H ₂ O (10 mol %), 5 min	71
11	DDQ, DMF, ^c <i>p</i> -TsOH·H ₂ O (50 mol %), 20 min	82
12	DMF, ^c <i>p</i> -TsOH·H ₂ O (1 equiv), 23 h	^e
13	DMF, ^c 23 h	^e

^aPerformed on 50 mg scale at 0.05 M. ^bIsolated product yield. ^cFlame-dried and flushed with N₂ reaction vessel. ^dStarting material decomposition. ^eNo reaction.

left the yield unchanged (entries 7 and 8). Employing *p*-toluenesulfonic acid (*p*-TsOH) as an additive improved the yield of **2a** to 83%, even in substoichiometric quantities (entries 9–11). Control reactions demonstrated the necessity of the oxidant for production of **2a** (entries 12 and 13).

With these optimized conditions in hand, we explored the substrate scope of the C–H activating group α to the sulfur (R², **1a–q**, Figure 1). Aromatic activating groups gave moderate to high yields with the exception of the pyridine substrate, which provided decomposition (**2a–e**). Ether (**2f**), ester (**2g**) and simple alkyl (**2h**) groups were not successful, due to either their lack of reactivity or instability. In contrast, the more activating cyclopropyl group gave a moderate yield of product **2i**. This result encouraged us to try an oxirane substituent, but it decomposed without providing the desired product **2j**. We then screened various alkene-activating groups (**2l–n**), and most produced a low yield of 1,4,2-oxathiazole with the exception of the cinnamyl group that gave 68% yield of **2k**. Because most alkene activating groups gave slower reaction times, we propose that the low yields obtained are due to the insufficient activation of the starting material rather than the lack of stabilization of the intermediate. The prolonged reaction times likely facilitate the decomposition of the 1,4,2-oxathiazole products, which would explain the low yields. Finally, we explored alkynes as the activating group; however, this functionality was not stable to the reaction and provided no product **2q** (Figure 1).

Variation of the thiohydroxamic acid substituent was then explored (R¹, **1r–z**). Aromatic (**2r**) and substituted aromatic (**2s**) substrates gave high yields of 1,4,2-oxathiazoles, while heteroaromatic substrates did not perform as well (**2t–v**). Cinnamyl thiohydroxamic acid and alkyl thiohydroxamic acids were well tolerated and provided moderate to high yields of 1,4,2-oxathiazoles (**2w**, **2x**, and **2y**). Finally, the reactive ester functional group smoothly underwent cyclization and provided **2z** in 68% yield, which provides a useful handle for further functionalization.

During the evaluation of the substrate scope, we performed the reaction with *O*-methyl *S*-benzyl thiohydroxamic acid **3** in

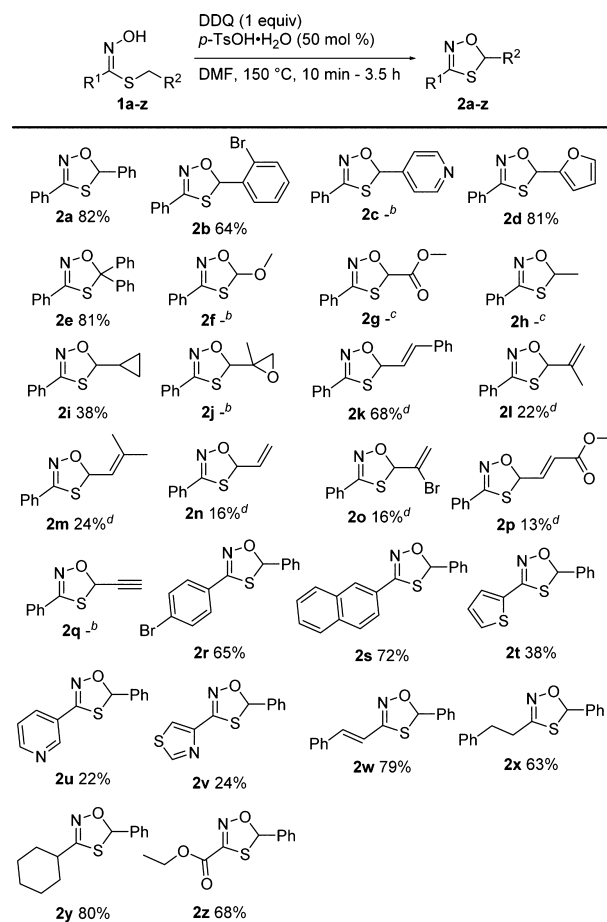


Figure 1. Substrate scope of 1,4,2-oxathiazole formation. Performed on 100 mg scale at 0.05 M: (b) decomposition of starting material; (c) no reaction; (d) no *p*-TsOH was used.

order to investigate the reaction mechanism (Figure 2, eq 1). Indeed, the oxidative cyclization could be triggered by two distinct mechanisms: (1) the oxidation of the oxime to an iminoxyl radical followed by a 1,5-hydrogen atom abstraction of the activated C–H bond^{9,11} or (2) the direct oxidation of the

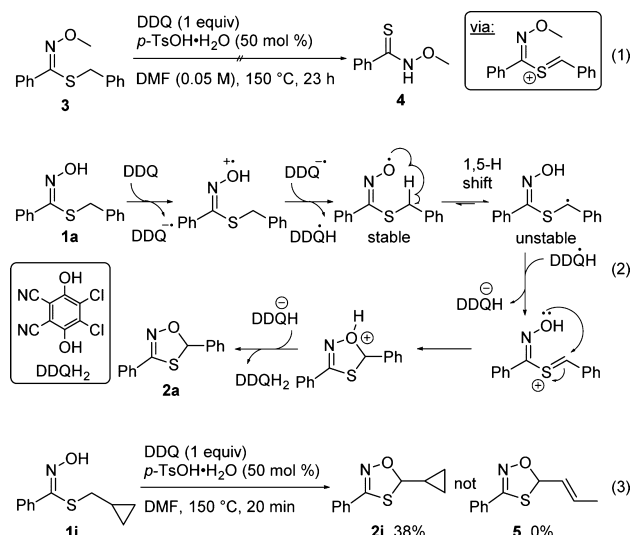


Figure 2. Mechanistic study (1), proposed mechanism (2), and radical clock reaction (3).

activated benzylic position α to the sulfur followed by the nucleophilic attack by the oxime.¹² To explore the potential mechanisms, we subjected **3** to our reaction conditions to evaluate the ability of DDQ to oxidize the benzylic position in the absence of an N-OH moiety. After prolonged reaction times, we observed no 1,4,2-oxathiazole product **2a** as well as no thiohydroxamic acid **4** as would be expected if a thiocarbenium ion was formed (**3** was reisolated in >75% recovery). Therefore, we propose that the reaction proceeds via a 1,5-hydrogen atom shift between the C-H α to the sulfur and the iminoxyl radical (Figure 2, eq 2). Iminoxyl radicals are known to be relatively stable radicals that undergo this type of hydrogen shift producing more reactive carbon radicals in a reversible manner.^{9,11} Moreover, sulfur is known to stabilize α -radicals and carbocations.¹³ Interestingly, thiohydroxamic acid **1i** containing the well-known cyclopropyl radical clock gave the unopened cyclopropyl product **2i** and not **5** as would be expected if a radical was formed α to the sulfur (Figure 2, eq 3). This result could be rationalized by the possibility that the radical is oxidized by DDQ faster than the rearrangement can occur or that the sulfur sufficiently stabilizes the radical/carbocation to prevent the opening of the cyclopropyl group.¹⁴

We also evaluated the scalability of the oxidative cyclization (Figure 3, eq 1). We performed the reaction with *S*-benzyl

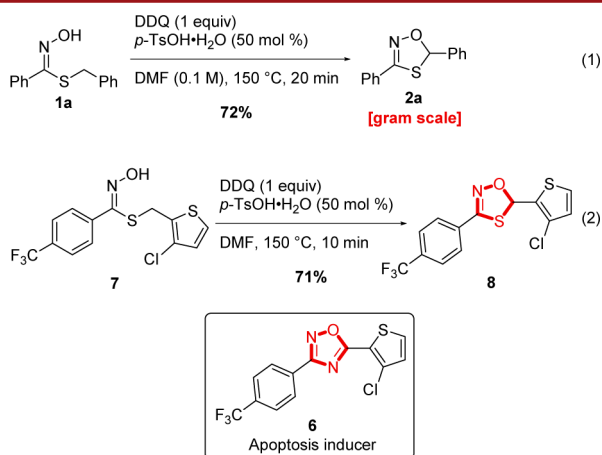


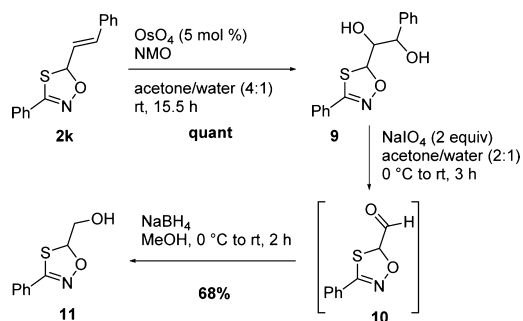
Figure 3. Scale-up of the oxidative cyclization (1) and 1,2,4-oxadiazole analog formation (2).

thiohydroxamic acid **1a** on 1 g scale and at 0.1 M concentration. We were pleased to obtain **2a** in 72% yield, highlighting the practicality of this method for building block synthesis. In order to demonstrate the utility of our method for analog synthesis, we applied it to the synthesis of the 1,4,2-oxathiazole analog **8** of a 1,2,4-oxadiazole anticancer lead compound **6** (Figure 3).¹⁵ Gratifyingly, subsection of **7** to our optimized conditions provided analog **6** in 71% yield (Figure 3, eq 2).

Finally, we evaluated the further functionalization of our 1,4,2-oxathiazole products (Scheme 2). 1,4,2-Oxathiazole **2k** could be converted to the corresponding alcohol **11** very efficiently in three steps and 68% yield, highlighting the versatility of our products and their utility as building blocks for synthesis. Indeed, in our hands 1,4,2-oxathiazoles are stable to acidic reaction conditions, aqueous basic workup, silica gel chromatography, hydrogenation conditions, and oxidative reaction conditions.

In conclusion, we have developed a novel method to access SH-1,4,2-oxathiazoles via the oxidative cyclization of readily

Scheme 2. Functionalization of 1,4,2-Oxathiazole **2k**



available thiohydroxamic acids. The method provides access to currently unavailable 1,4,2-oxathiazoles bearing a wide range of functional groups in up to 82% yield and is amenable to gram scale synthesis. Importantly, this method represents the only practical way to access these heterocycles that could be of great utility for medicinal chemists as new scaffolds for SAR studies of their related nitrogen and oxygen containing heterocycles. Our initial studies show the potential of our method for analog synthesis and building block preparation, and further efforts in these areas will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02256.

Experimental procedures, characterization of products, ¹H and ¹³C NMR spectra (PDF)
Crystallographic information for **2a** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.
- (2) (a) Argyropoulos, N. G. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol. 6, pp 105–144. (b) Dickoré, K.; Wegler, R. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 970. (c) Maignan, J.; Vialle, J. *Bull. Soc. Chim.* **1973**, *6*, 1973. (d) Huisgen, R.; Mack, W. *Chem. Ber.* **1972**, *105*, 2815. (e) Chung, W.-S.; Tsai, T.-L.; Ho, C.-C.;

Chiang, M. Y. N.; le Noble, W. J. *J. Org. Chem.* **1997**, *62*, 4672.
(f) Feddoui, A.; Ittoa, M. Y. A.; Hasnaouia, A.; Villeminb, D.; Jaffrès, P.-A.; De Oliveira Santos, J. S.; Riahid, A.; Huet, F.; Daran, J.-C. *J. Heterocycl. Chem.* **2004**, *41*, 731. (g) Altintas, O.; Glassner, M.; Rodriguez-Emmenegger, C.; Welle, A.; Trouillet, V.; Barner-Kowollik, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 5777.

(3) Hemming, K. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol 5, pp 243–314.

(4) Cooper, N. J. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2005; Vol 3, pp 355–396.

(5) (a) Irfan, I.; Sawangjaroen, N.; Bhat, A. R.; Azam, A. *Eur. J. Med. Chem.* **2010**, *45*, 1648. (b) Cai, J.; Wei, H.; Hong, K. H.; Wu, X.; Zong, X.; Cao, M.; Wang, P.; Li, L.; Sun, C.; Chen, B.; Zhou, G.; Chen, J.; Ji, M. *Bioorg. Med. Chem.* **2015**, *23*, 3457.

(6) (a) Burkett, B. A.; Kane-Barber, J. M.; O'Reilly, R. J.; Shi, L. *Tetrahedron Lett.* **2007**, *48*, 5355. (b) Burkett, B. A.; Fu, P.; Hewitt, R. J.; Ng, S. L.; Toh, J. D. W. *Eur. J. Org. Chem.* **2014**, *2014*, 1053. (c) Lim, Y. W.; Hewitt, R. J.; Burkett, B. A. *Eur. J. Org. Chem.* **2015**, *2015*, 4840.

(7) (a) Lemerrier, B. C.; Pierce, J. G. *J. Org. Chem.* **2014**, *79*, 2321. (b) Lemerrier, B. C.; Pierce, J. G. *Org. Lett.* **2014**, *16*, 2074.

(8) (a) Praly, J.-P.; Boyé, S.; Joseph, B.; Rollin, P. *Tetrahedron Lett.* **1993**, *34*, 3419. (b) Nagy, V.; Benlifa, M.; Vidal, S.; Berzsényi, E.; Teihet, C.; Czifrák, K.; Batta, G.; Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. *Bioorg. Med. Chem.* **2009**, *17*, 5696.

(9) Zhang, F.-L.; Wang, Y.-F.; Chiba, S. *Org. Biomol. Chem.* **2013**, *11*, 6003.

(10) For a more detailed optimization table, see Table S1 in the [Supporting Information](#).

(11) (a) Zhu, X.; Wang, Y.-F.; Ren, W.; Zhang, F.-L.; Chiba, S. *Org. Lett.* **2013**, *15*, 3214. (b) Shi, D.; Qin, H.-T.; Zhu, C.; Liu, F. *Eur. J. Org. Chem.* **2015**, *2015*, 5084. For a review on C-sp³ oxidation by iminoxyl radicals, see: (c) Chiba, S.; Chen, H. *Org. Biomol. Chem.* **2014**, *12*, 4051.

(12) DDQ has been shown to oxidize activated C–H bonds and create a heteroatom-stabilized electrophile that can be trapped by a nucleophile: (a) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (b) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184. (c) Cui, Y.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 1720. (d) Rimaz, M.; Khalafy, J.; Badali, M.; Slepokura, K.; Lis, T.; Souldozi, A.; Ramazani, A.; Joo, S. W. *J. Struct. Chem.* **2013**, *54*, 217. (e) Bhunia, S.; Ghosh, S.; Dey, D.; Bisai, A. *Org. Lett.* **2013**, *15*, 2426. (f) Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. *Org. Lett.* **2015**, *17*, 1684. (g) Gillard, R. M.; Sperry, J. *J. Org. Chem.* **2015**, *80*, 2900.

(13) (a) Luedtke, A. E.; Timberlake, J. W. *J. Org. Chem.* **1985**, *50*, 268. (b) Korth, H. G.; Sustmann, R.; Groninger, K. S.; Leisung, M.; Giese, B. *J. Org. Chem.* **1988**, *53*, 4364.

(14) (a) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69. (b) Peh, G.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 5614.

(15) Zhang, H.-Z.; Kasibhatla, S.; Kuemmerle, J.; Kemnitzer, W.; Ollis-Mason, K.; Qiu, L.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2005**, *48*, 5215.