Organic LETTERS

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Synthesis of Thiazolines by Copper Catalyzed Aminobromination of Thiohydroximic Acids

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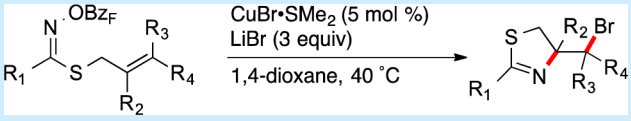
Supporting Information

ABSTRACT: A copper catalyzed aminobromination of alkene tethered thiohydroximic acids is described, providing a rapid approach to unnatural thiazoline scaffolds not readily available via existing methods. Moderate to high yields of bromothiazolines are obtained with alkyl- and aryl-substituted thiohydroximic acid building blocks containing mono-, di-, and trisubstituted alkenes. The reaction provides high levels of 5-exo selectivity, and terminally monosubstituted alkenes result in predominant syn-diastereoselectivity.



Thiazolines are important heterocycles present in many natural products and biologically active compounds such as curacin A,[1] an antimitotic agent; largazole,[2] an HDAC inhibitor; and bacitracin A,[3] an antibiotic used in topical ointments and in animal feed. Moreover, thiazoline-containing natural products are found in aromas, flavors, and luminescent molecules such as D-luciferin, which is responsible for the bioluminescence of fireflies. The D-luciferin/luciferase system and analogues have been extensively studied and used for in vivo imaging.[4] Thiazolines have also been used as chiral ligands for asymmetric catalysis and chiral ionic liquids as their thiazolidinium salts.[5] Due to their importance in numerous fields of research, many synthetic efforts have been devoted toward their synthesis.[6] Common methods for thiazoline synthesis employ β-amino alcohol or β-amino thiol derivatives as starting materials, and these approaches are straightforward when the required alcohol or thiol is readily available. However, further substitution at the 4-position and compounds not arising from natural amino acids require multistep preparation of the required amino-alcohols or are prepared through alkylation of simpler derivatives[7] (Figure 1). Therefore novel methods to access substituted thiazolines in a rapid and stereoselective fashion are needed.

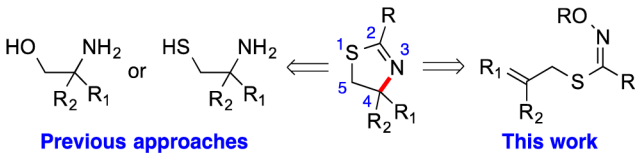
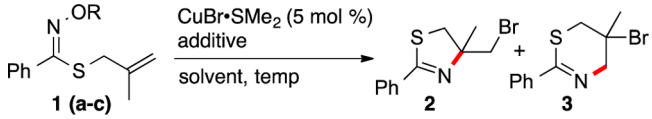


Figure 1. Approaches to thiazoline synthesis.

As part of our program to investigate the synthetic utility of thiohydroxamic acids and their derivatives as synthetic building blocks, we envisioned employing thiohydroximic acids to form thiazolines via intramolecular amination. Oxime derivatives have been shown to form iminyl radicals that readily cyclize onto an appended alkene to generate dihydropyrrole derivatives.[8] Amidine derivatives have also been shown to form amidinyl radicals that cyclize to form imidazoline derivatives.[9] Building on this precedent we began an exploration into the copper-catalyzed[10] aminobromination of thiohydroximic acids to prepare thiazolines.

Thiohydroximic acid derivatives were prepared in a two-step, one-pot process via *S*-alkylation/*O*-acylation of the corresponding thiohydroxamic acids.[11] With these building blocks in hand we began exploring their reactivity in copper catalyzed aminobromination reactions (Table 1). Initially we chose to employ the disubstituted alkene derivative **1** (**a**–**c**) since this substrate would represent a difficult compound for the proposed reaction due to a competing 6-endo cyclization pathway. Employing copper(I) bromide dimethylsulfide as our catalyst, we screened N–O bond activating groups (R, Table 1), additives, solvents, and temperatures. Although methyl substituted derivatives proved unreactive (entry 1, Table 1)

Table 1. Optimization of the Aminobromination Reaction



no.	R[a]	conditions[b]	2 (%)[c]	3 (%)[c]
1	Me (**1a**)	LiBr (3 equiv), dioxane, 24 h	–	–
2	Bz (**1b**)	LiBr (3 equiv), dioxane, 3 h	23	3
3	Bz	dioxane, 3 h	3	–
4	Bz	LiOBz (3 equiv), dioxane, 3 h	–	–
5	Bz_F (**1c**)	LiBr (3 equiv), dioxane, 45 min	27	6
6	Bz_F	LiBr (3 equiv), toluene, 4 h	21	21
7	Bz_F	LiBr (3 equiv), DCE, 24 h	27	18
8	Bz_F	LiBr (3 equiv), dioxane, 6 h[d]	52	12

[a]Bz = benzoyl; Bz_F = pentafluorobenzoyl. [b]Performed at 80 °C on a 50 mg scale. [c]Isolated yields. [d]Performed at 40 °C.

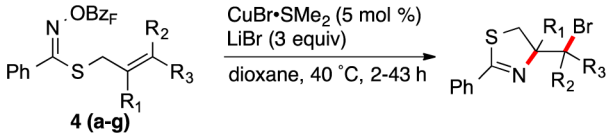
Received: February 24, 2014
Published: March 19, 2014

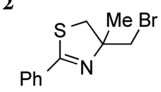
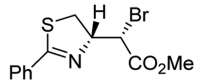
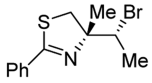
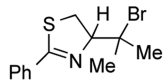
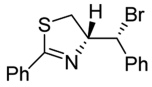
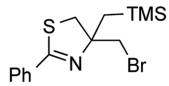
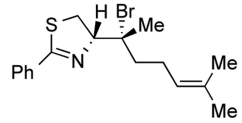
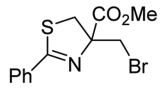
   dx.doi.org/10.1021/ol500588v | *Org. Lett.* 2014, 16, 2074–2076

both benzoyl (entry 2, Table 1) and pentafluorobenzoyl (entries 5–8, Table 1) proved to effectively activate the N–O bond for cleavage, with the pentafluoro compounds allowing for remarkably mild reaction conditions (entry 8, Table 1).[12,13] The addition of lithium bromide proved critical for turnover of the catalyst and dioxane was the solvent of choice, paralleling the optimized conditions for oxime cyclizations.[8b] Significant improvement was achieved by conducting the reaction at 40 °C (vs 80 °C), and reaction yields generally were improved on scale (>200 mg) to provide **2** in 50% yield (entry 8, Table 1) with 12% of the six-membered compound being formed under these conditions. We felt that compound **2** served as a rigorous test of this chemistry and were gratified to observe a successful reaction with thiohydroximic acid **1c**.[14]

With optimized conditions in hand we explored the substrate scope of the alkene group (Table 2). Subjection of

Table 2. Scope of Alkene Substitution



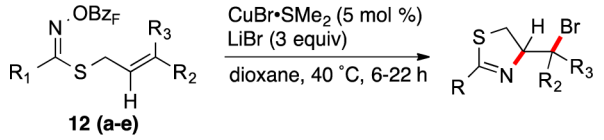
product	yield (%)	product	yield (%)
2 	50	**8** 	69[d]
5 	61[a]	**9** 	77[e]
6 	91[b]	**10** 	42
7 	58[c]	**11** 	0[f]

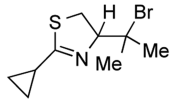
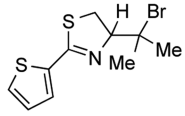
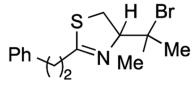
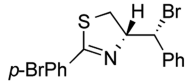
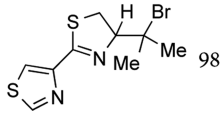
[a]2:1 mixture of diastereomers. [b]Single diastereomer (X-ray). [c]One diastereomer. [d]6.7:1 mixture of diastereomers. [e]10:1 inseparable mixture with thiazole. [f]Slow decomposition of SM was observed.

thiohydroximic acids **4a–g** to the copper(I) conditions provided a range of substituted thiazolines in moderate to high yields.[15] Terminally monosubstituted alkenes provided a high level of *cis*-diastereoselectivity (**5–8**, Table 2), which was confirmed by X-ray analysis of compound **6** (see Supporting Information). The high syn-diastereoselectivity observed in this reaction points to a mechanism in which copper remains coordinated to the iminyl radical and alkene partner to deliver the bromide from the same face.[16] Thiohydroximic acids bearing alkene (**7**), ester (**8**), and TMS (**10**) substituents were well tolerated to provide functionalized thiazoline products poised for further derivatization. Unfortunately, the substrate bearing an ester substituent at the R_1 position did not yield the desired thiazoline **11** even under forcing conditions.[17]

Variation of the thiohydroximic acid substituent was then explored (Table 3). Both aliphatic (**13** and **14**, Table 3) and

Table 3. Scope of Thiohydroximic Acid Substitution



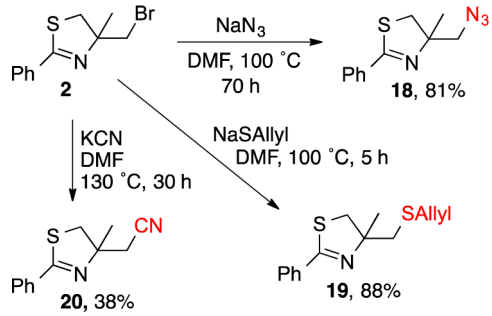
product	yield (%)	product	yield (%)
13 	52	**16** 	61[a]
14 	63	**17** 	87[b]
15 	98		

[a]10:1 inseparable mixture with thiazole. [b]Single diastereomer.

heteroaromatic (**15** and **16**, Table 3) groups smoothly underwent cyclization and provided bromothiazoline products in good yields. Of particular interest is the excellent yield for thiazole–thiazoline product **15** due to the frequent incorporation of this motif in bioactive natural products.[2,18] In addition to heteroaromatic products, *p*-bromophenyl derivative **17** underwent aminobromination in excellent yield.

Finally, we evaluated the feasibility of further functionalization of the bromothiazoline products. Subjection of **2** to sodium azide, allylthiol, or potassium cyanide provided the corresponding substitution products in moderate to excellent yields (**18–20**, Scheme 1). These reactions highlight the versatility of the thiazoline products and provide access to molecules with handles for further derivatization.

Scheme 1. Substitution of Bromothiazoline 2



In conclusion, we have developed a new synthesis of thiazolines bearing a range of functional groups in good yields and diastereoselectivities. These initial studies on thiohydroximic acids demonstrate their potential as building blocks in organic synthesis. Furthermore, the bromothiazoline products are useful compounds for both medicinal and materials applications. Further explorations into the potential of thiohydroxamic acids as reagents for heterocycle construction, optimization of the copper-catalyzed aminobromination

dx.doi.org/10.1021/ol500588v | *Org. Lett.* 2014, 16, 2074–2076

reaction, and development of an asymmetric process will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of products, ^{1}H and ^{13}C NMR spectra, and the CIF file for **6** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge North Carolina State University for generous start-up support, and acknowledgement is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research. Mass spectra were obtained at the Mass Spectrometry Laboratory at North Carolina State University. We thank Dr. Roger Sommer (NCSU) for X-ray crystallographic analysis of **6**.

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(14) Thiohydroxamic and thiohydroximic acids have been reported to have limited stability to both N−O bond activation and heating (due to rearrangement processes). In our hands, we found these compounds to be remarkably stable to all but the most forceful conditions and bench stable for months.

(15) The lower yields of some bromothiazolines are a result of the formation of byproducts such as thiazolines with a terminal alkene derived from an elimination reaction and thiols derived from a Beckmann rearrangement.

(16) The extent in which copper plays a role in the reaction after the initial N−O bond cleavage has not been well studied (refs 8b and 9b). This work represents the first use of internal alkenes in such iminyl-type radical cyclizations to generate potential mixtures of diastereomers.

(17) In general, electron-withdrawing substituents at the internal alkene position were not tolerated in this chemistry and electron-deficient alkenes that were successful had a significantly slower reaction rate. These results suggest an intermediate iminyl radical with electrophilic character; for discussion, see: (a) Le Tadic-Biadatti, M.-H.; Callier-Dublanchet, A.-C.; Horner, J. H.; Quiclet-Sire, B.; Zard, S. Z.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 559. (b) Guindon, Y.; Guérin, B.; Landry, S. R. *Org. Lett.* **2001**, *3*, 2293. (c) Chi, Y.-J.; Yu, H.-T. *Comput. Theor. Chem.* **2013**, *1005*, 75.

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