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One-Pot Strategy for Thiazoline Synthesis from Alkenes and Thioamides

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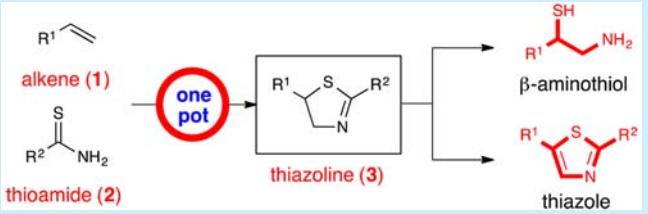
Supporting Information

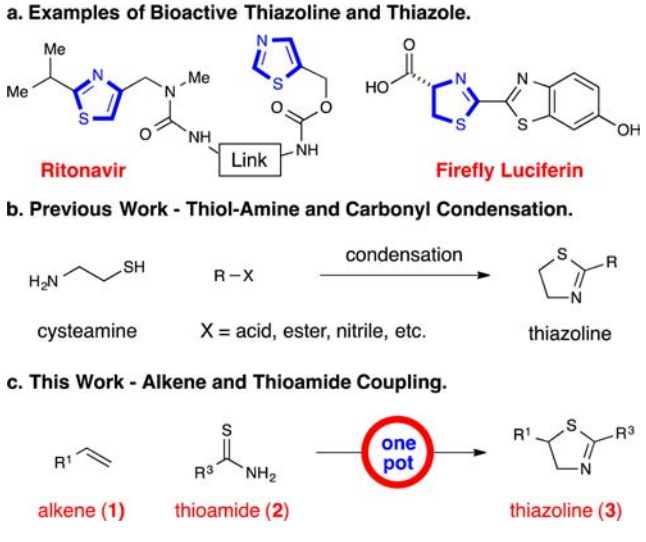
ABSTRACT: A convenient synthesis of a privileged pharmaceutical motif, thiazoline is accomplished. This reaction utilizes simple and readily available alkene and thioamide substrates in an intermolecular fashion via a simple one-pot procedure. A wide range of functional groups is tolerated, and the thiazoline product has been further utilized for the synthesis of the corresponding β-aminothiol and thiazole from routine hydrolysis and oxidation protocols.



Expediting access to heterocycles, common structural motifs in natural products and pharmaceuticals, directly from simple feedstock is an attractive synthetic strategy. Nitrogen- and sulfur-containing thiazolines and their derivatives are important classes of compounds owing to their frequent appearances in bioactive natural products and pharmaceuticals.[1] These molecules often exhibit a wide range of bioactivities including anticancer, anti-HIV, antibiotic, and neurological activities.[2] For example, ritonavir, an antiretroviral drug containing two thiazoles, has been indicated to treat HIV.[2d] Firefly luciferin is also well known for its role in the bioluminescence of fireflies (Scheme 1a).[3] In addition, a number of interesting natural products such as largazole, curacin A, and tantazole B contain one or more thiazoline subunits.[4] Moreover, thiazolines have also been utilized as ligands in transition-metal-catalyzed coupling reactions.[5] To gain access to this useful heterocyclic core, several synthetic methods have been established.[6] Currently, the condensation of cysteamine with nitriles, esters, or imidates represents the method of choice for thiazoline synthesis (Scheme 1b). However, limited availability of the β-aminothiols often hinders the versatility of this method in accessing a diverse array of thiazolines, particularly when potential structure−activity relationship (SAR) studies are desired. Oftentimes, multistep syntheses are required to gain access to the desired aminothiol precursor. To partially circumvent the β-aminothiol availability problem, methods involving condensation of β-amino alcohols with carbonyl surrogates, followed by thionation of the amide intermediate, and eventual ring closure to provide the thiazolines have also been developed.[7] Finally, intramolecular strategies or α-halo carbonyl precursors have also been utilized to construct the thiazoline core.[8]

Alkenes are highly versatile synthetic substrates for classic reactions such as epoxidation, dihydroxylation, bromination, etc. The synthetic utility of alkenes is further augmented by their availability from commercial sources or reliable synthetic operations.[9] A range of thioamides are also commercially available or readily synthesized from their amide counterparts with sulfurating agents.[10] To circumvent the β-aminothiol availability problem in thiazoline synthesis, the development of a general coupling reaction between alkenes and thioamides would provide versatile access to a wide array of thiazoline structures (Scheme 1c).[11] Herein, we report our findings of a convenient one-pot reaction of alkenes and thioamides to enable the construction of a variety of thiazolines in addition to demonstrating the derivatizations of the thiazoline product to useful thiol-amine and thiazole motifs.

Scheme 1. Direct Coupling of Alkene and Thioamide



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We initially hypothesized that generation of 1,2-dibromoalkanes from halogenation of alkenes could be followed by nucleophilic additions of thioamides to afford the desired thiazoline products. Although 1,2-dihalogenoalkanes were often considered as poor electrophiles due to competing elimination or alkene reversion reactions, the utilization of a soft nucleophile such as a thioamide in the absence of a strong base might alleviate these deleterious pathways.[12] To validate our hypothesis, we synthesized 1,2-dibromoethylbenzene in 94% yield from simple dibromination of styrene **1a** in acetonitrile. To our delight, when the 1,2-dibromoalkane was treated with thiobenzamide **2a**, thiazoline **3a** formation was observed in 63% yield in acetonitrile at 80 °C (Figure 1). This

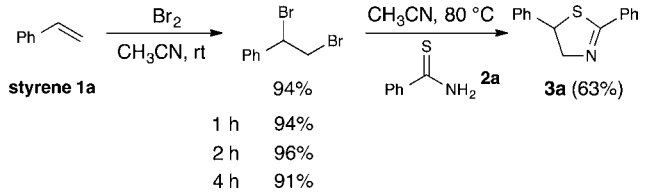
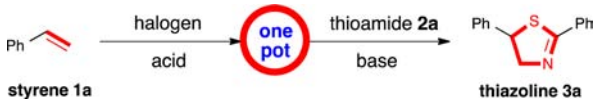


Figure 1. Validation of hypothesis.

result clearly demonstrated that a common solvent acetonitrile could be used for both 1,2-dibromoalkane formation and subsequent nucleophilic displacements; thus, suggesting a one-pot procedure directly from simple alkene precursors was indeed plausible. A time study showed that the dibromination reaction went to completion within 1 h. Therefore, the one-pot reaction was conducted by adding the thioamide to the dibromoethylbenzene mixture after 1 h. Gratifyingly, this procedure produced the desired thiazoline **3a** in 39% yield, validating our initial hypothesis (Table 1, entry 1).

Interested in further optimizing this reaction, we considered the utilization of alternative bromine sources. Specifically, in situ generated bromine equivalent by oxidation of halide salts was attractive by avoiding the use of corrosive bromine. This oxidative strategy had been extensively utilized for the bromination of alkenes and arenes.[13] A combination of lithium bromide (LiBr) and aqueous hydrogen peroxide was selected as a starting point. Using this approach, the thiazoline product was produced in only 7% yield (Table 1, entry 2). The presence of an acid additive was crucial to promote the yield to 50%, presumably to promote the oxidation of the halide salts (Table 1, entry 3). Further time optimization revealed that the dibromination of styrene went to completion within 1 h. Screening different halides and oxidants demonstrated that the LiBr and urea·hydrogen peroxide (UHP) combination was the optimal choice to provide 56% desired product (Table 1, entries 3−7). Solvent and acid evaluation showed that acetonitrile (1 M) and 2 equiv of trifluoroacetic acid (TFA) gave the highest yield (Table 1, entries 8−13). We reasoned that perhaps residual acid from the dibromination process could be detrimental to the subsequent nucleophilic substitution reactions. To validate this hypothesis, a base was added along with the thioamide nucleophile. Indeed, addition of 2 equiv of LiOAc improved the yield to 60% (Table 1, entry 14). Encouraged by this result, a series of mild inorganic bases and fine-tuning of base stoichiometry were examined to further increase the yield to 69%, with 3 equiv of $NaHCO_3$ being the most optimal (Table 1, entries 14−19). Finally, increasing the halide source to 3.0 equiv provided the best yield for this reaction at 73% (Table 1, entry 20). Increasing the

Table 1. Optimization of Reaction Conditions[a]



entry	halogen	acid	solvent	base	yield (%)
1	Br_2		CH_3CN		39
2	$LiBr/H_2O_{2(aq)}$		CH_3CN		7
3	$LiBr/H_2O_{2(aq)}$	TFA	CH_3CN		50
4	LiBr/oxone	TFA	CH_3CN		6
5	LiBr/UHP	TFA	CH_3CN		56
6	NaBr/UHP	TFA	CH_3CN		21
7	KBr/UHP	TFA	CH_3CN		11
8	LiBr/UHP	TFA	DMF		10
9	LiBr/UHP	TFA	DCE		2
10	LiBr/UHP	TFA	toluene		25
11	LiBr/UHP	AcOH	CH_3CN		52
12	LiBr/UHP	TsOH	CH_3CN		23
13[b]	LiBr/UHP	TFA	CH_3CN		52
14	LiBr/UHP	TFA	CH_3CN	LiOAc	60
15	LiBr/UHP	TFA	CH_3CN	NaOAc	66
16	LiBr/UHP	TFA	CH_3CN	Na_2CO_3	60
17	LiBr/UHP	TFA	CH_3CN	$NaHCO_3$	66
18[c]	LiBr/UHP	TFA	CH_3CN	$NaHCO_3$	44
19[d]	LiBr/UHP	TFA	CH_3CN	NaHCO3	69
20[e,f]	LiBr/UHP	TFA	CH_3CN	$NaHCO_3$	73 (71)
21[e,g]	LiBr/UHP	TFA	CH_3CN	$NaHCO_3$	66
22[e,h]	LiBr/UHP	TFA	CH_3CN	$NaHCO_3$	49

[a]Reaction conditions: styrene **1a** (1.0 equiv, 0.5 mmol), halide (2.2 equiv), oxidant (1.0 equiv), acid (2.0 equiv), solvent (1 M) at 80 °C for 1 h, then thioamide **2a** (3.0 equiv) and base (3.0 equiv) for 15 h at 80 °C. 1,3-Benzodioxole is used as the internal standard. [b]TFA (1.5 equiv). [c]$NaHCO_3$ (1.0 equiv). [d]$NaHCO_3$ (3.0 equiv). [e]Conditions: LiBr (3.0 equiv), UHP (1.5 equiv), $NaHCO_3$ (3.0 equiv). [f]Isolated yield in parentheses. [g]CH_3CN (1.5 M). [h]50 °C.

concentration or lowering the temperature, however, lead to decreased efficiency (Table 1, entries 21 and 22).

With the optimized conditions in hand, the alkene substrate scope was evaluated. As the examples below illustrate, a notable feature of this reaction was the ability to introduce a broad range of thioamides without decomposition by the bromine source. A range of styrene derivatives achieved moderate to good yields of the desired thiazolines (Scheme 2, entries **3a−i,l**).[14] For example, substitutions at the para position of the benzene ring with electron-neutral or -donating groups worked efficiently (Scheme 2, products **3a−c,f,l**). On the other hand, tethering an electron-withdrawing group at the para position resulted in diminishing yield (Scheme 2, product **3d**). Additionally, halogen substitutions at either the ortho or para position produced good yields of the thiazolines (Scheme 2, products **3e,g−i**). Aliphatic alkenes with alkyl, alcohol, ether, ester, and imide functionalities were also viable substrates in this reaction (Scheme 2, products **3j,k,m−r**). In terms of regioselectivity for the aliphatic alkenes, the initial nucleophilic addition was reversed compared to the styrene derivatives presumably due to the primary C−Br bond being the more electrophilic site for aliphatic alkenes, whereas the secondary benzylic C−Br bond is the more electrophilic position for the styrene derivatives.

For the thioamide substrate scope, substitution of a methyl group at either the ortho or para position afforded the products in good yields (Scheme 3, products **4a** and **4b**). Electron-

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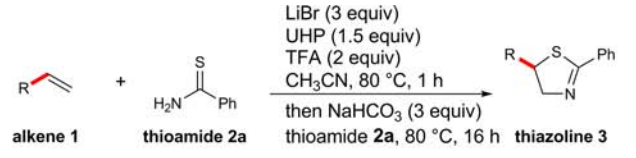
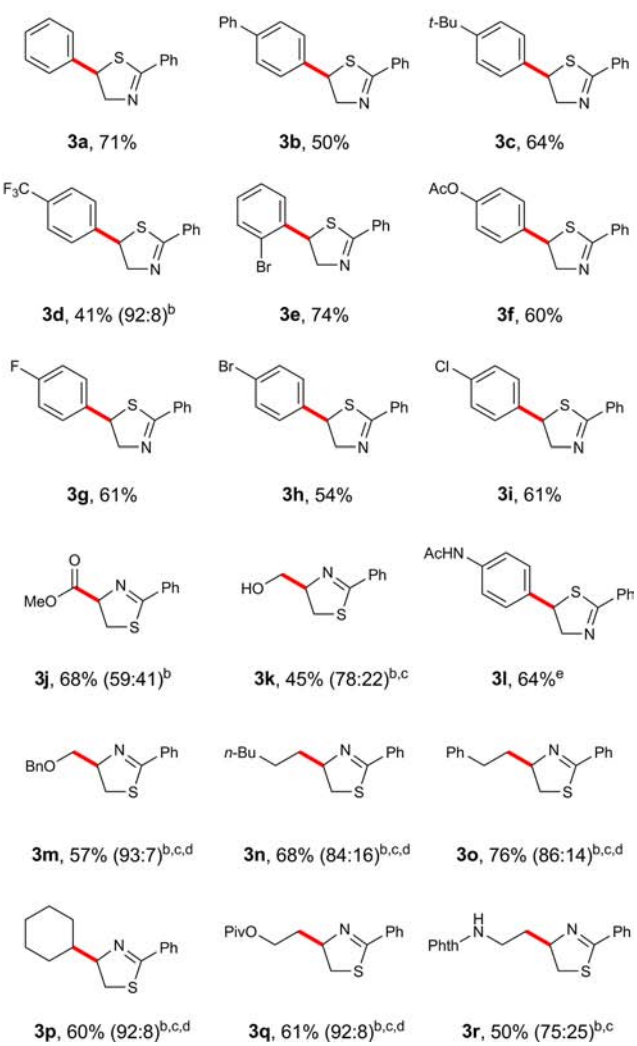
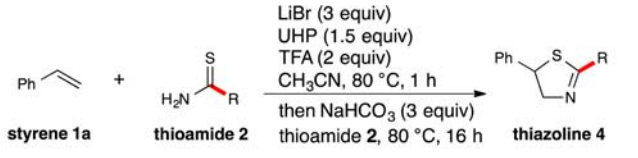
Scheme 2. Alkene Substrate Scope[a]

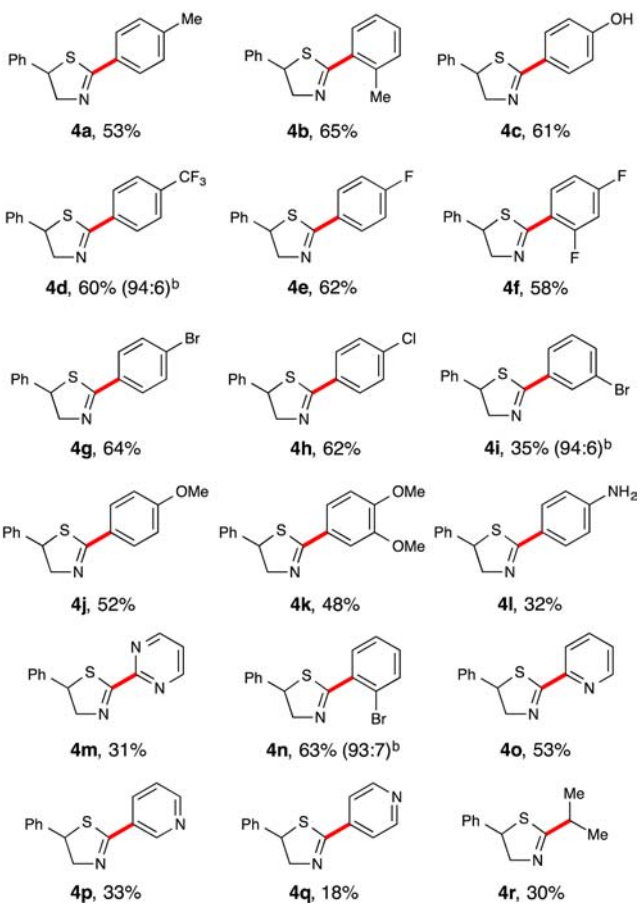




[a]Standard reaction condition unless otherwise noted. For detailed conditions, see the Supporting Information. [b]Major regioisomer was shown. Regioisomeric ratios were determined by crude NMR and >95:5 unless noted in parentheses. [c]Propionitrile, 100 °C. [d]Several minor regioisomers were isolated and reported as **3m′**, **3n′**, **3o′**, **3p′**, and **3q′**. [e]Bromine was used for the dibromination reaction.

Scheme 3. Thioamide Substrate Scope[a]





[a]Standard reaction condition unless otherwise noted. For detailed conditions, see the Supporting Information. [b]Major regioisomer is as shown. Regioisomeric ratios are determined by crude NMR and >95:5 unless noted in parentheses.

donating groups such as alcohol, ether, and amine proceeded in moderate yields (Scheme 3, products **4c,j,l**). In addition, halogen substitutions at the ortho, meta, or para positions afforded the thiazoline products in good efficiency while containing functionalities for further synthetic operation (Scheme 3, products **4e−i,n**). Moreover, thioamides including electron-deficient aromatics such as pyridines and pyrimidine could also provide the desired products, albeit in lower yields (Scheme 3, products **4m,o−q**). Notably, 2-pyridinethioamide proceeded smoothly to afford a structure resembling a common ligand framework. Furthermore, inclusion of these heteroaromatic examples demonstrated the versatility of this methodology in providing beneficial structures for potential SAR studies. Finally, alkylthioamide could also furnish the respective thiazoline compound (Scheme 3, entry **4r**).

After demonstrating a broad substrate scope for thiazoline synthesis, we set out to explore its utility in further synthetic elaborations. In this case, gram-scale synthesis of **3a** was accomplished in 61% yield using the standard reaction conditions (Figure 2). Upon refluxing **3a** in 5 M HCl, hydrolysis of the ring structure occurred to generate the desired *β*-aminothiol **5** in 92% yield, thus providing an efficient two-step method for the highly regioselective thioamination of terminal alkenes.[15] On the other hand, oxidation of **3a** by DDQ in dichloromethane provided the heteroaromatic thiazole **6** in 95% yield.[16] These derivatizations offered pathways to a number of useful nitrogen-containing compounds, further highlighting the synthetic advantages of this one-pot procedure.

In conclusion, we have developed a practical and reliable procedure for the synthesis of thiazolines by oxidatively coupling alkenes and thioamides. This intermolecular reaction

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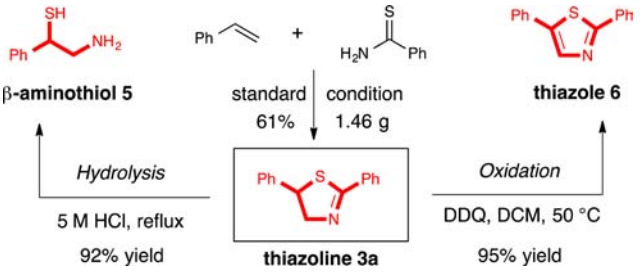

Figure 2. Derivatizations of thiazoline.

renders the synthesis of a wide array of thiazoline structures possible while containing functional groups capable of further synthetic elaborations. In addition, examples of derivatizing the thiazoline core to the corresponding β-aminothiol or thiazole via hydrolysis or oxidation, respectively, have been demonstrated. Most importantly, the limitation in β-aminothiol availability from condensation methods can be addressed by the utilization of simple and readily available alkene and thioamide substrates using this one-pot procedure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00079.

Experimental procedure and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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