

## Mild Method for the Synthesis of Thiazolines from Secondary and Tertiary Amides

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Thiazolines are a class of heterocycles that have received much attention recently due to their presence in numerous interesting biologically active natural products such as curacin A,<sup>1</sup> thiangazole,<sup>2</sup> and mirabazole B<sup>3</sup> (Figure 1). Even though numerous methodologies are available,<sup>4–10</sup> high yields for the formation of the thiazoline are sometimes not obtained, especially with acid-sensitive or racemization-prone substrates. Herein, we report that at low temperatures in a medium buffered with excess pyridine, iminium (2)<sup>11</sup> and imino triflates (3)<sup>12</sup> can be generated by the treatment of tertiary or secondary amides with triflic anhydride. We reasoned that subsequent addition of an amino thiol to these highly electrophilic species should result in the formation of the thiazoline under conditions that most functional groups and chiral centers should tolerate (Scheme 1).

Pioneering studies by Ghosez and others have demonstrated that iminium (2)<sup>11</sup> and imino triflates (3)<sup>12</sup> can be generated by the treatment of tertiary or secondary amides with triflic anhydride. We reasoned that subsequent addition of an amino thiol to these highly electrophilic species should result in the formation of the thiazoline under conditions that most functional groups and chiral centers should tolerate (Scheme 1).

The optimal conditions involved an initial activation of the amide by adding triflic anhydride to the amide in

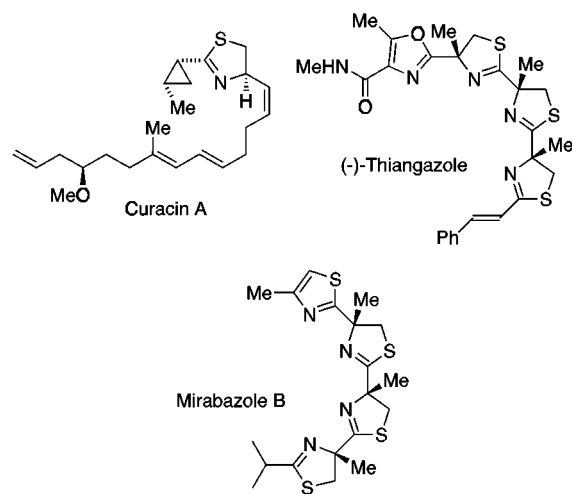
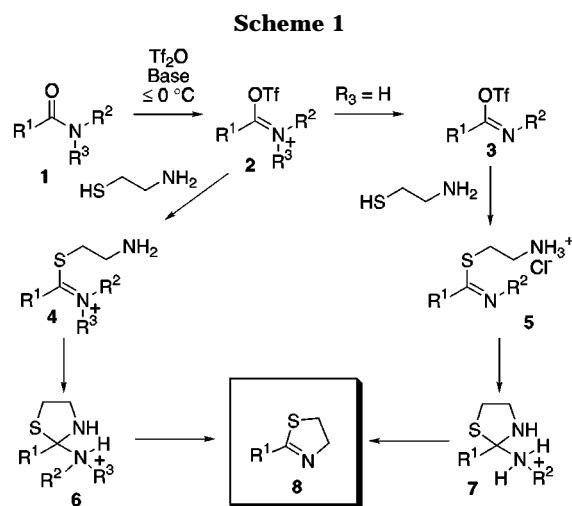


Figure 1.



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anhydrous dichloromethane-containing pyridine, which is present to neutralize any adventitious acid. Pyridine seems to be the optimal base since using a stronger base than pyridine generates a conjugate acid that would be too weak to be an effective general acid catalyst for the addition of the amine onto the thio imidate or for the elimination of the amine residue. Addition of triflic anhydride must be slow since an exotherm can cause triflic anhydride to react with pyridine to form *N*-triflylpyridinium triflate, which is not reactive enough to *O*-sulfonylate the amide.

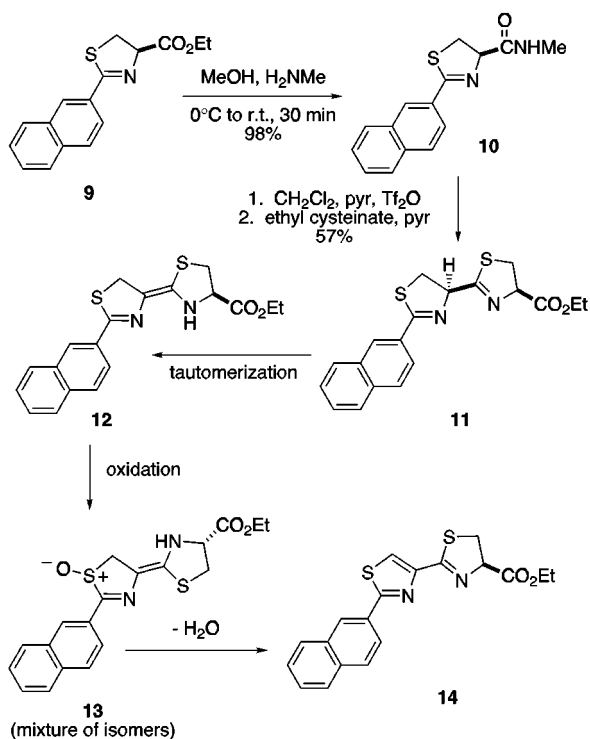
Application of these conditions to various amides are summarized in Table 1. Secondary and tertiary alkyl and aryl amides are readily converted to thiazolines. The reaction of the substrate derived from 2-phenylcyclopropane carboxylic acid seems to be sensitive to the nature of the amide. The secondary *N*-methylamide is converted efficiently (entries 9 and 10), but the tertiary *N,N*-dimethyl amide decomposes and fails to give the thiazoline. This may be attributed to the propensity of the cinnamyl cyclopropane moiety to undergo carbocationic ring opening. The cyclopropyl thiazoline was formed without any detectable epimerization at the  $\alpha$ -carbon. In all the cases studied, no epimerization at the  $\alpha$ -carbon of cysteine was detected when optically pure cysteine ethyl ester was used as the amino thiol.

To demonstrate the mildness of these reaction conditions, several more highly functionalized amides were converted

**Table 1. Conversion of Secondary and Tertiary Amides to Thiazolines<sup>a</sup>**

		$\text{R}^1-\text{C}(=\text{O})-\text{N}(\text{R}^2)(\text{R}^3) \xrightarrow[\text{2) amino-thiol, pyridine, -30}^\circ\text{C to r.t.}]{\text{1) CH}_2\text{Cl}_2, \text{pyridine, Tf}_2\text{O, -50 to 0}^\circ\text{C}}$							
				$\text{R}^1-\text{C}(\text{S})=\text{N}-\text{R}^4$					
				Amino-thiol A $\text{R}^4 = \text{H}$ Amino-thiol B $\text{R}^4 = \text{CO}_2\text{Et}$					
Entry	Amide	Amino-Thiol	Product	Yield	Entry	Amide	Amino-Thiol	Product	Yield
1		A		91 %	8		B		58 % <sup>b</sup>
2		B		90 % <sup>b</sup>	9		A		72 %
3		A		72 %	10		B		77 % <sup>d</sup>
4		B		91 % <sup>b</sup>	11		B		76 % <sup>b</sup>
5		B		55 % <sup>c</sup>	12		B		73 % <sup>b</sup>
6		A		71 % <sup>c</sup>	13		B		80 % <sup>d</sup>
7		B		65 % <sup>b</sup>					

<sup>a</sup>The typical procedure was used in all cases. <sup>b</sup>No racemization was observed. <sup>c</sup>The racemic amide was used as starting material. <sup>d</sup>>30:1 diastereomeric purity.

**Scheme 2**

to thiazolines (entries 11–13). Using typical reaction conditions, amides bearing functional groups such as a benzoate, silyl ether, benzyl ether, and acetonide were readily converted to thiazolines.

Another interesting application of this methodology would be the synthesis of molecules containing multiple contiguous thiazolines such as thianguazole (Scheme 2). Thiazoline ester **9** was quantitatively converted to *N*-methyl amide **10** upon

treatment with excess methylamine in methanol. Amide **10** was then submitted to the standard conditions, but this did not produce the desired bis(thiazoline) **11** as the final product. Instead, two other compounds were isolated. The first compound was the result of tautomerization followed by subsequent oxidation of the desired bis(thiazoline) **11**.<sup>13</sup> Small quantities of this unstable ester **13** could be isolated as a mixture of diastereomers, but this compound eventually rearranged to a less polar compound upon chromatography. This less polar compound turned out to be the thiazole **14**,<sup>14</sup> and it is presumably the product of the aromatization of ester **13** upon the loss of H<sub>2</sub>O. Although this unoptimized reaction failed to give the desired bis(thiazoline) **11**, isolable bis(heterocyclic) compounds were produced in 57% yield, thus demonstrating that this methodology is capable of forming contiguous thiazolines.

Whereas the mono(thiazoline) compounds are relatively stable, bis(thiazoline) compounds made from  $\alpha$ -amino acids with  $\alpha$ -protons readily tautomerize to give compounds that seem to be more sensitive toward oxidation or decomposition. Applications of this method toward the synthesis of curacin A, thianguazole, and mirabazole are underway and will be reported in due course.

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**Supporting Information Available:** Characterization data and proton and carbon NMR spectra for all compounds (57 pages).

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