An Aluminum(III)-Catalyzed Thioamide–Aldehyde–Styrene Condensation: Direct Synthesis of Allylic Thioamide Derivatives

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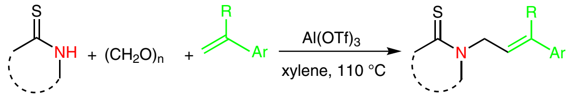

1. cyclic and acyclic thioamides
2. transition-metal-free
3. direct allylation of thioamides

19 examples
up to 86% yield

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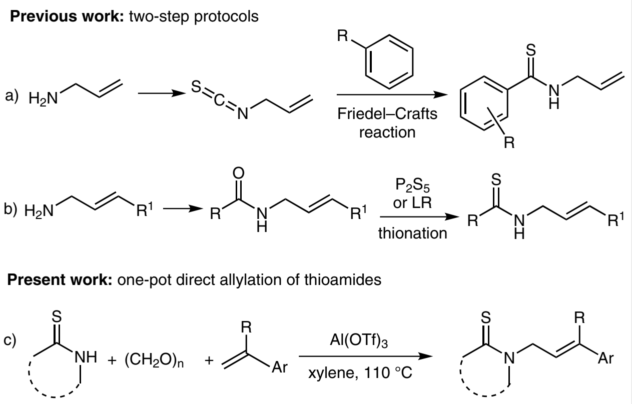
Abstract An aluminum(III) triflate catalyzed three-component synthesis of allylic thioamide derivatives by condensation of a thioamide, paraformaldehyde and a styrene is reported.

Key words thioamides, paraformaldehyde, styrenes, allyl thioamides, multicomponent reactions, condensation

Allylamines form a significant class of biologically active nitrogen compounds, and the allylamine skeleton is found in various natural products and drugs.[1–6] Moreover, allylamines are fundamental building blocks in organic chemistry and have been used as starting materials for the synthesis of numerous compounds, such as amino acids, alkaloids, and carbohydrate derivatives.[7–10] Consequently, the synthesis of allylamine derivatives has attracted considerable interest among researchers.[11–21]

The thioamides and their derivatives are also an important class of biologically and pharmaceutically active compounds.[22] Allylic thioamides are particularly important,[23,24] especially in regio- and stereoselective preparations of 4,5-dihydro-1,3-thiazoles.[25] Therefore, the development of methods for synthesizing allylic thioamide derivatives is essential in organic chemistry.

N-Allylbenzothioamides can be prepared by the reaction of aromatic compounds, under Friedel–Crafts reaction conditions, with 3-isothiocyanatoprop-1-ene, prepared from allylamine (Scheme 1, a).[26] However, few methods have been developed for the synthesis of *N*-(3-substituted)allyl thioamides; the most widely used method is thionation of an allylic amide with phosphorus pentasulfide or Lawesson's reagent (LR; Scheme 1, b).[27] To the best of our knowledge, there are no reports in the literature on the direct synthesis of allylic thioamides from thioamide derivatives as substrates. Here, we present a useful method for the preparation of allylic thioamides by direct allylation of thioamides (Scheme 1, c).

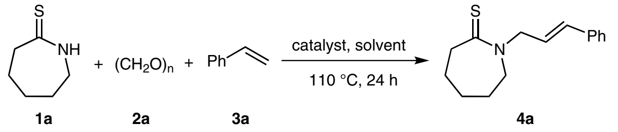


Scheme 1 Methods for the synthesis of allylic thioamides

Our group's recent research has been devoted to the development of simple and efficient methods for preparing allylamine derivatives, and we have developed a general protocol for the direct N-allylation of electron-deficient amides by Lewis acid catalyzed amide–aldehyde–alkene condensation reactions.[28–31] On the basis of our previous work, we developed an efficient strategy for the synthesis of allylic thioamide derivatives by an Al(OTf)$_3$-catalyzed thioamide–aldehyde–alkene reaction. In this reaction, we successfully constructed C–N and C–C bonds in one pot without any additives. Furthermore, the use of an aluminum(III) salt as a cheap and abundant catalyst increases the attractiveness of this method.

Initially, we examined the three-component reaction of azepane-2-thione (**1a**), paraformaldehyde (**2a**) and styrene (**3a**) as a model reaction (Table 1). When we used our previous reaction conditions[29,31] with I_2 or $Bi(OTf)_3$ as the catalyst, no reaction occurred (Table 1, entries 1 and 2). When the iron catalysts $Fe(OTf)_3$, $Fe(acac)_3$, and $FeCl_3$ were tested, $FeCl_3$ promoted the three-component reaction to give the desired product **4a** in 10% yield (entries 3–5). In contrast, combinations of I_2 with Fe catalysts [$I_2/Fe(OTf)_3$ and $I_2/FeCl_3$/TBAB] promoted the conversion into **4a** in 21% and 51% yield, respectively (entries 6 and 7). Interestingly, I_2 combined with TfOH successfully promoted the reaction to deliver an 82% yield of **4a** (entry 8), whereas the reaction catalyzed by $Al(OTf)_3$ gave **4a** in 86% yield (entry 9). When the loading of $Al(OTf)_3$ was decreased to 10 mol%, a considerably lower yield was obtained (entry 10). Finally, we examined the effect of the solvent on this reaction and found that xylene gave better results than $MeNO_2$ or 1,4-dioxane (entries 11 and 12). The reaction is therefore best conducted with $Al(OTf)_3$ (20 mol%) as the catalyst and xylene as the solvent at 110 °C for 24 hours.

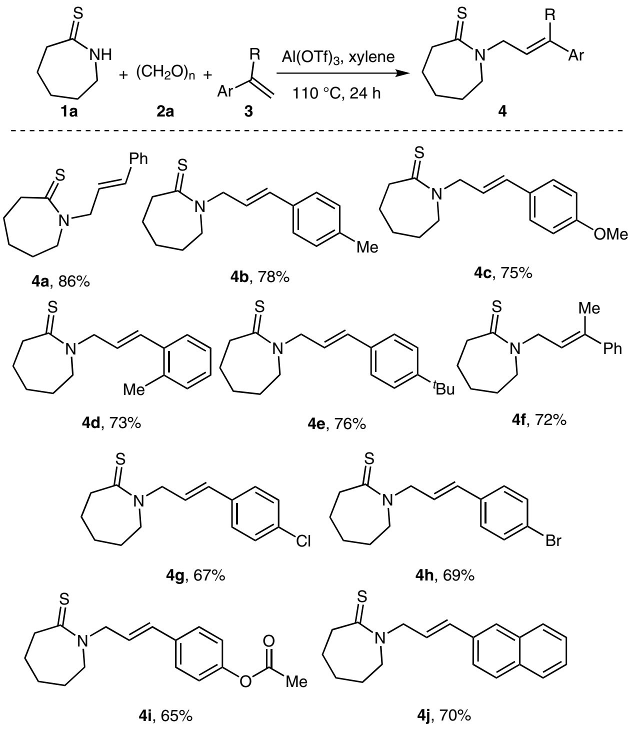
Table 1 Optimization of Conditions for the Three-Component Reaction[a]



Entry	Catalyst (mol%)	Solvent	Yield[b] (%)
1	I_2 (200)	xylene	0
2	$Bi(OTf)_3$ (20)	xylene	0
3	$Fe(OTf)_3$ (20)	xylene	0
4	$Fe(acac)_3$ (20)	xylene	0
5	$FeCl_3$ (20)	xylene	10
6	I_2 (30)/$Fe(OTf)_3$ (5)	xylene	21
7	I_2 (20)/$FeCl_3$ (20)/TBAB (20)	xylene	52
8	I_2 (20)/TfOH (10)	xylene	82
9	$Al(OTf)_3$ (20)	xylene	86
10	$Al(OTf)_3$ (10)	xylene	76
11	$Al(OTf)_3$ (20)	$MeNO_2$	57
12	$Al(OTf)_3$ (20)	1,4-dioxane	68

[a] Reaction conditions: **1a** (1 mmol), **2a** (4 mmol), **3a** (1.2 mmol), solvent (3 mL), 110 °C, 24 h.
[b] Isolated yield after column chromatography.

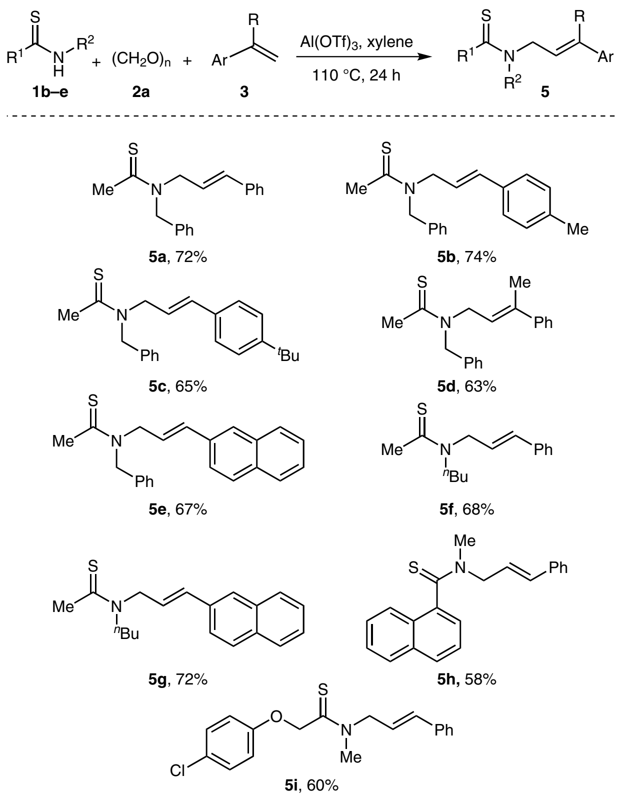
Next, we applied the optimized protocol to the allylation of the cyclic thioamide **1a** with paraformaldehyde (**2a**) and various styrenes **3** (Scheme 2).[32] The reaction proved to be relatively broad in scope, tolerating a variety of steric and electronic changes in the styrene reaction partner to give products **4a**–**j** in good yields. Reactions of styrenes bearing electron-donating groups (Me, OMe, or *t*-Bu) on the phenyl ring gave the corresponding products **4b**–**e** in higher yields than those of products **4g**–**i** from styrenes containing electron-withdrawing groups (Cl, Br, or OAc). Note that both *ortho*- and *para*-substituted styrenes as substrates gave the desired products **4d** and **4e** in good yields, indicating that the steric effects of the methyl and *tert*-butyl group are negligible. α-Methylstyrene as a substrate also reacted smoothly to give the corresponding allylic thioamide derivative **4f** in 72% yield. Furthermore, electron-deficient 2-vinylnaphthalene also reacted successfully to give the corresponding product **4j** in 70% yield.



Scheme 2 Three-component reactions of azepane-2-thione (**1a**), paraformaldehyde (**2a**), and various styrenes

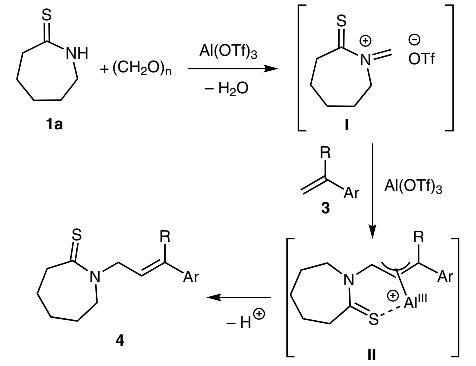
To further expand the range of thioamide products, we explored the three-component reactions of acyclic thioamides **1b**–**e**, paraformaldehyde (**2a**), and styrenes **3** (Scheme 3).[33] The reactions proceeded smoothly to give the corresponding products in good yields. Acyclic thioamides bearing *N*-benzyl, *N*-butyl, or *N*-methyl substituents gave the corresponding allylic thioamide derivatives **5a**–**i** in good yields. The existence of thioamide **5h** as a mixture of isomers due to restricted rotation around the thioamide bond was confirmed by ^1H NMR and ^{13}C NMR spectroscopy; however, the two isomers could not be separated by simple column chromatography.

We also examined the reactions of ethyl oxoacetate, as well as those of other aryl aldehydes such as 4-nitro-, 4-fluoro-, 4-bromo-, and 4-methylbenzaldehydes; however, no reactions were observed, and further optimization of the conditions might be needed.



Scheme 3 Three-component reactions of acyclic thioamides, paraformaldehyde (**2a**), and styrenes

The mechanism of the reaction might be as follows: First, the reaction of the aldehyde with the thioamide **1a** in the presence of Al(III) generates the corresponding iminium ion **I** (Scheme 4). Subsequently, **I** is attacked by the styrene **3** to generate the carbocationic intermediate **II**. Finally, the carbocation **II** undergoes selective β-proton elimination, accompanied by loss of Al(III), to give the allylic thioamide derivative **4**.



Scheme 4 Proposed mechanism for the Al-catalyzed direct allylation through thioamide–aldehyde–alkene condensation

In summary, we have developed an Al(OTf)$_3$-catalyzed three-component reaction of thioamides with paraformaldehyde and styrenes to give a series of allylic thioamide derivatives. Both cyclic and acyclic thioamides participate in the reaction, and we successfully achieved the construction of a C–N and a C–C bond in one pot by using a simple catalyst system without any additives. Furthermore, the reaction tolerates a wide range of thioamides and styrenes as reaction partners and it gives good to excellent yields. The present method should prove to be a useful tool in the synthetic chemistry of allylic thioamides.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562507.

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(32) **1-[(2*E*)-3-Phenylprop-2-en-1-yl]azepane-2-thione (4a); Typical Procedure**

An oven-dried tube was charged with a mixture of cyclic thioamide **1a** (1 mmol, 0.129 g), paraformaldehyde (**2a**; 4 mmol, 0.120 g), styrene (**3a**; 1.2 mmol, 0.125 g), and Al(OTf)$_3$ (20 mol%, 0.191 g). Anhydrous xylene (3 mL) was added from a straw, and the mixture was stirred at 110 °C for 24 h while the reaction was monitored by TLC. The mixture was cooled to r.t., and the reaction was quenched with sat. aq NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 × 15 mL) and the organic layers were combined, washed with brine, and dried ($MgSO_4$). The crude product was purified by column chromatography [silica gel, PE–EtOAc (1:6)] to give a yellow oil; yield: 211 mg (0.86 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 6.49 (d, *J* = 15.6 Hz, 1 H), 6.18–6.11 (m, 1 H), 4.16 (d, *J* = 5.2 Hz, 2 H), 3.34 (s, 2 H), 2.57 (d, *J* = 5.2 Hz, 2 H), 1.66 (d, *J* = 38.4 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 136.6, 132.5, 128.5, 127.5, 126.3, 125.1, 49.8, 48.6, 37.1, 29.9, 28.4, 23.4. HRMS (ESI$^+$): *m/z* [M + H]$^+$ calcd for $C_{15}H_{20}NS$: 246.1311; found: 246.1316.

(33) ***N*-Benzyl-*N*-[(2*E*)-3-Phenylprop-2-en-1-yl]ethanethioamide (5a); Typical Procedure**

An oven-dried tube was charged with a mixture of acyclic thioamide **1b** (1 mmol, 0.165 g), paraformaldehyde (**2a**; 4 mmol, 0.120 g), styrene (**3a**; 1.2 mmol, 0.125 g), and Al(OTf)$_3$ (20 mol%, 0.191 g). Anhydrous xylene (3 mL) was added from a straw, and the mixture was stirred at 110 °C for 24 h while the reaction was monitored by TLC. The mixture was cooled to r.t., and the reaction was quenched with sat. aq NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 × 15 mL) and the organic layers were combined, washed with brine, and dried ($MgSO_4$). The crude product was purified by column chromatography [silica gel, PE–EtOAc (1:6)] to give a yellow oil; yield: 202 mg (0.72 mmol, 72%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 10 H), 6.43 (t, *J* = 16.2 Hz, 1 H), 6.19–6.05 (m, 1 H), 4.65 (s, 1 H), 4.54 (s, 1 H), 4.16 (d, *J* = 6.6 Hz, 1 H), 3.99 (d, *J* = 5.4 Hz, 1 H), 2.20 (d, *J* = 27.0 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9, 133.1, 131.9, 128.9, 128.7, 128.6, 128.5, 128.2, 127.9, 127.7, 127.6, 127.4, 126.4, 124.5, 123.8, 50.9, 49.5, 48.1, 47.3, 21.7, 21.6. HRMS (ESI$^+$): *m/z* [M + H]$^+$ calcd for $C_{18}H_{20}NS$: 282.1311; found: 282.1314.