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Chemoselective Transition-Metal-Free Acylation of Thioamides by N–C(S) Bond Cleavage using Acyclic Twisted Thioamides

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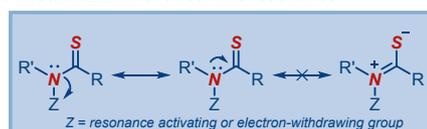
A new method for chemoselective transition-metal-free acylation of thioamides with ketones by N–C(S) bond cleavage is reported. The approach exploits acyclic twisted thioamides to accomplish selective thio-Claisen condensation by ground state-destabilization of the thioamide bond. The valuable 3-hydroxy-1-thioxoketone products are obtained from bench-stable thioamide precursors under mild transition-metal-free, room temperature conditions. Various ground-state-destabilized thio-amides are amenable to this selective thio-acylation protocol. The method advances the reactivity of twisted thioamides to C–C bond forming reactions under transition-metal-free conditions.

Introduction

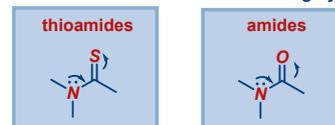
Thioamides as the closest ‘single-atom’ isosteres of the amide bond have attracted major attention in chemical synthesis owing to their unique chemical properties and biological relevance resulting from the presence of lipophilic sulfur.¹ Simultaneously, recent years have witnessed an explosion of interest in activation of amide bonds by N–C(O) cleavage,² wherein this reactivity manifold has addressed the historical challenge of selective cleavage of amidic linkage characterized by strong $n_N \rightarrow \pi_{C=O}$ conjugation (15–20 kcal/mol) in planar amides.³ However, in sharp contrast to amides, the activation of N–C(S) bonds in thioamides represents even a more formidable challenge owing to the higher resonance of thioamides as a result of the increased resonance contribution of the polar form. Furthermore, the geometric properties of thioamides, including the large radius of sulfur, impart the rotational barrier around the N–C(S) axis much higher than that around the corresponding N–C(O) bond in amides by up to 7 kcal/mol.⁴ Overall, these factors contribute to the much slower kinetics for breaking the N–C(X) bond of thioamides vs. amides, and as a consequence very few methods for selective activation of thioamides have been reported.⁵

Moreover, recent studies highlight the privileged role of sulfur in drug discovery,⁶ where at present one-third of active

Ground-state-destabilization of thioamide resonance



Thioamides: ‘single-atom’ amide bond bioisosteres: highly useful & challenging



- N–C(S) vs. N–C(O) rotational barrier: 22 vs. 17 kcal/mol
- S vs. O van der Waals radius: 1.85 vs. 1.40 Å
- C=S vs. C=O length: 1.71 vs. 1.23 Å
- C=S vs. C–O electronegativity: 2.58 vs. 3.44

Transition-metal-free thio-Claisen C–C bond formation: this study

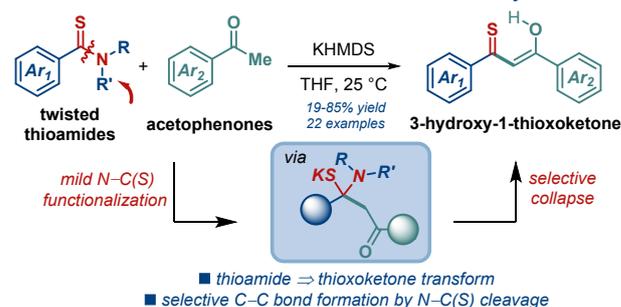


Figure 1. Ground-State-Destabilization of Thioamides.

pharmaceutical ingredients feature sulfur,⁷ while the selective activation of N–C(S) bonds in thioamides could offer unparalleled opportunities in manipulation of thioamide bonds by pathways orthogonal to electrophilic additions, desulfurizations and soft enolizations.⁸

Over the past decade, our laboratory has pioneered the amide bond activation manifold by ground-state-destabilization.^{9,10} This pathway enables to deploy generic acyclic twisted amides in a variety of activation manifolds and

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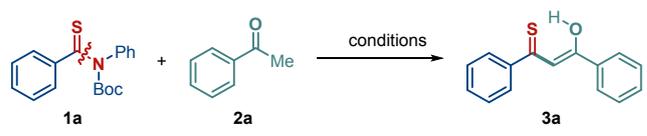
has been broadly adopted by chemists worldwide. Recently, we hypothesized that the major advantages of ground-state-activation of amides should be amenable to thioamide bonds to enable generic and synthetically-useful N–C(S) bond activation with for broad applications in organic, medicinal and materials chemistry. There are very few examples of transition-metal-free reactions of ground-state-destabilized thioamides reported to date.^{5a-5c} The term ground-state-destabilization refers to a combination of lowering resonance of thioamides by (1) the conformation of thioamides, where the amino group is not coplanar with the C=S group, and (2) the lower delocalization of the lone pair by an electronic conjugation on the adjacent N-functional group. In addition, there is an effect of lower electronegativity of the sulfur atom compared to oxygen. In this respect, we reported C–N^{5a,5b} and C–O^{5c} bond formation by selective cleavage of thioamide bonds. As a continuation of our studies, herein, we report that thioamides can be applied to highly chemoselective C–C bond formation by transition-metal-free acylation with ketones by selective N–C(S) bond cleavage (Figure 1). This method permits to obtain valuable 3-hydroxy-1-thioxoketone products from bench-stable thioamide precursors under mild transition-metal-free, room temperature conditions. In a broader view, the method opens the door for the utilization of ground-state-destabilized thioamides for a plethora of C–C bond forming reactions by selective N–C(S) cleavage.

Results and discussion

Our investigation commenced with the examination of thio-Claisen reaction of N-Boc/Ph thioamide (**1a**) with acetophenone as a model system (Table 1). After significant experimentation, we obtained a 70% yield of the product using KHMDS (2.5 equiv) as a base in THF, but further analysis revealed it to be the enol tautomer, 3-hydroxy-1-thioxoketones, rather than the expected 1,3-thioxoketone (entry 1). The reaction proceeded with full chemoselectivity for the N–C(S) bond cleavage with products resulting from alternative bond cleavages and hydrolysis not detected. Furthermore, evaluation of other solvents revealed that toluene (entry 2) and Et₂O (entry 3) were also suitable media for the reaction, however, the yield decreased. In contrast, more polar solvents, such as DMF, NMP and DMSO (entries 4-6) as well as nonpolar solvents, such as CH₂Cl₂ (entry 7) were ineffective. Furthermore, we examined the effect of temperature and found that the yield gradually decreased at higher temperatures (entries 8-10), consistent with deactivation of twisted thioamides by N-Boc-deacylation. Interestingly, we found that various bases can be used as promoters, including NaH, NaHMDS, NaOtBu and KOtBu, (entries 11-14). In contrast, LiOtBu, Cs₂CO₃, K₂CO₃, Na₂CO₃ and K₃PO₄ were ineffective in this process (entries 15-19). The structure of the 3-hydroxy-1-thioxoketone (**3a**) was confirmed by x-ray crystallographic analysis (Figure 2, CCDC 2346234) and revealed that the product exists in an O-enol form.¹¹ The length of the C=S bond is 1.680 Å, while the length of the C–OH bond is 1.316 Å. The 3-hydroxy-1-thioxoketone is co-planar with the S=C–C–C dihedral angle of 2.09° and HO–C–C–C dihedral angle

of 1.70°. The S–H distance is 2.087 Å and the O–H–S angle is 155.0°, indicating hydrogen bonding.

Table 1. Optimization of Reaction Conditions^a



entry	base	solvent	yield ^b (%)
1	KHMDS	THF	70
2	KHMDS	Toluene	38
3	KHMDS	Et ₂ O	38
4	KHMDS	DMF	trace
5	KHMDS	NMP	trace
6	KHMDS	DMSO	trace
7	KHMDS	CH ₂ Cl ₂	trace
8 ^c	KHMDS	THF	56
9 ^d	KHMDS	THF	47
10 ^e	KHMDS	THF	35
11	NaH	THF	64
12	NaHMDS	THF	41
13	NaOtBu	THF	25
14	KOtBu	THF	16
15	LiOtBu	THF	trace
16	Cs ₂ CO ₃	THF	trace
17	K ₂ CO ₃	THF	trace
18	Na ₂ CO ₃	THF	trace
19	K ₃ PO ₄	THF	trace

^aConditions: thioamide (0.20 mmol, 1.0 equiv), acetophenone (1.5 equiv), base (2.5 equiv), solvent (1.0 M), 25 °C, 15 h. ^bIsolated yield <40 °C. ^c60 °C. ^d80 °C.

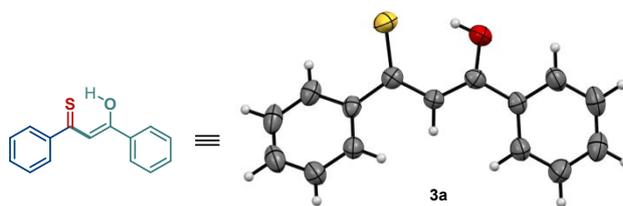
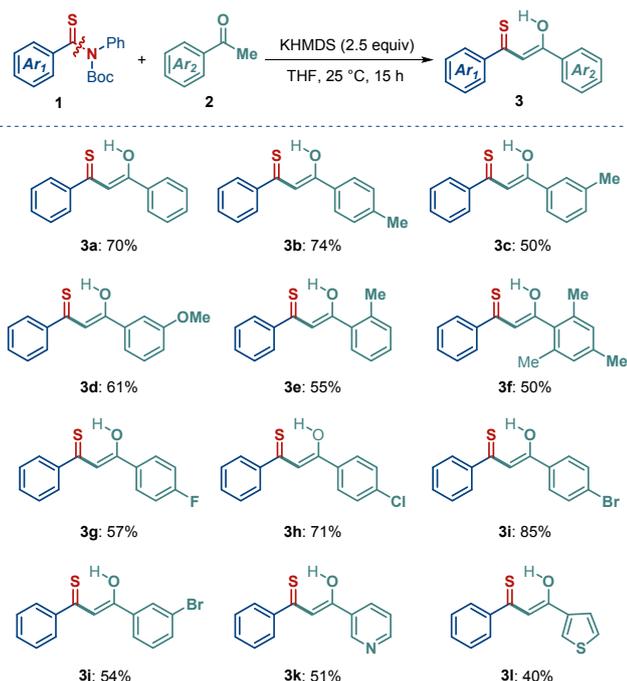


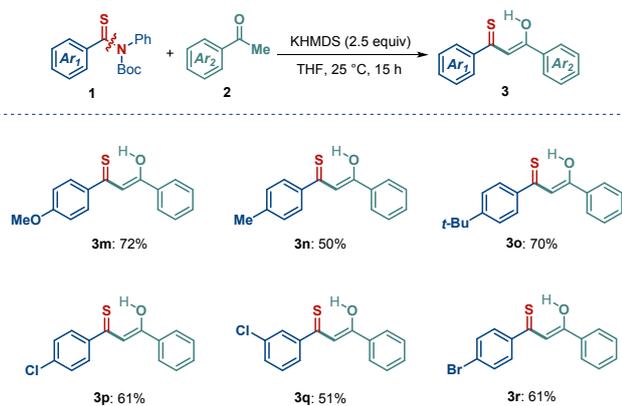
Figure 2. X-ray Structure of 3-hydroxy-1-thioxoketone (**3a**). CCDC 2346234.

With the optimized conditions in hand, we first tested the scope of aromatic ketones that are amenable to this thio-Claisen condensation (Scheme 1). As shown, we found that various electron-rich, electron-deficient and sterically-hindered acetophenones are suitable partners for this reaction. As such, substitution at the *para*- (**3b**), *meta*- (**3c–3d**) and *ortho*- (**3e–3f**) positions was well-tolerated, affording the aromatic 3-hydroxy-1-thioxoketone products in 50-74% yields. Furthermore, the reaction is compatible with sensitive halides, such as fluoro (**3g**), chloro (**3h**) and even bromo (**3i–3j**), providing functional handles for further manipulation. Moreover, this mild method can tolerate heterocycles, such as pyridines (**3k**) and thiophenes (**3l**), affording heteroaryl 3-hydroxy-1-thioxoketone with selectivity for N–C(S) activation. However, when reactions were conducted using propiophenone as the carbon nucleophile, the isolated yield was very low (<5%). This is because the α -hydrogen atoms in propiophenone are less acidic compared to

those in acetophenone, making it more difficult to form the enolate intermediate.



Scheme 1. Acylation of Thioamides by Chemoselective N-C(S) Cleavage: Scope of Aromatic Ketones. Conditions: thioamide (1.0 equiv), acetophenone (1.5 equiv), KHMDS (2.5 equiv), THF (1.0 M), 25 °C, 15 h. Isolated yields.

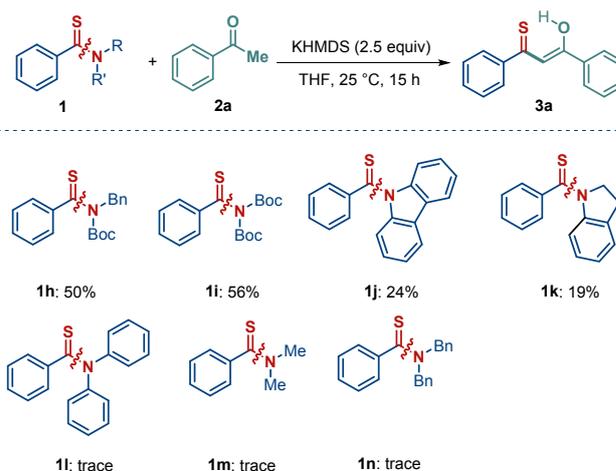


Scheme 2. Acylation of Thioamides by Chemoselective N-C(S) Cleavage: Scope of Thioamides. See SI for details.

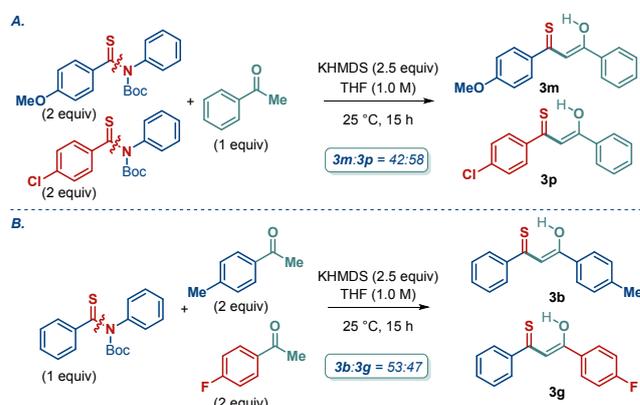
Next, the scope of the thioamide electrophiles was investigated (Scheme 2). As shown, we found that the method is compatible with electron-rich acyclic twisted thioamides, including methoxy (**3m**), alkyl (**3n**) and *t*-butyl (**3o**) substitution. Pleasingly, halides are also tolerated on the thioamide component, as illustrated by chloro (**3p–3q**) and even bromo (**3r**) substitution. Additionally, when reactions were conducted using acetophenones with nitro (-NO₂) and cyano (-CN) substituents, the yields were very low (<5%). This was due to the reduced nucleophilicity caused by the electron-withdrawing groups.

Next, the capacity of this thio-Claisen acylation was evaluated using different ground-state-destabilized thioamides (Scheme 3). In general, the activation of the thioamide N-C(S) bond can be accomplished by steric or electronic factors.

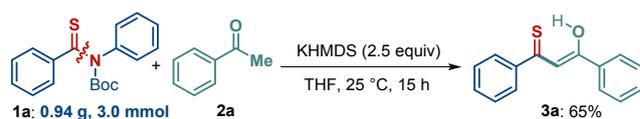
However, as is the case in the amide bond N-C(O) activation, the synthetically most useful is the single-N-Boc or double-N,N-



Scheme 3. Effect of Amide Distortion on Acylation of Thioamides by Chemoselective N-C(S) Cleavage. See SI for details.



Scheme 4. Competition Studies. See SI for details.



Scheme 5. Scale-Up Experiment. See SI for details.

Boc₂ activation, which enables to enlist common 1° and 2° precursors by selective *N*-*tert*-butoxycarbonylation. Pleasingly, we found that this thio-Claisen acylation can be applied to *N*-alkyl-Boc thioamides as well as *N,N*-Boc₂ thioamides.

Furthermore, studies were conducted to gain insight into the selectivity of this thio-Claisen condensation (Scheme 4). As expected, we found that more electron-deficient thioamides participate in the reaction preferentially (4-Cl:4-MeO, 58:42, Scheme 4A). Furthermore, electron-rich acetophenones are preferred (4-Me:4-F, 53:47). Overall, these findings are consistent with nucleophilic addition to twisted thioamides dictated by electrophilicity of the thioamide bond.

Finally, to demonstrate the scalability of the method, the reaction was performed on a 3.0 mmol scale (0.94 g) and

afforded the product in 65% yield (Scheme 5), demonstrating that the method is well-amenable to synthetic use and scale-up.

Conclusions

In conclusion, we have developed a new method for chemoselective transition-metal-free acylation of thioamides with ketones by N–C(S) bond cleavage. In contrast to amides, activation of the thioamide bond represents even a greater challenge due to increased resonance stabilization of the thioamidic linkage and the geometric properties of sulfur. The present study demonstrates that twisted thioamides can be applied as a platform to selectively form C–C bonds by nucleophilic acylation. The valuable 3-hydroxy-1-thioxoketone products are obtained from bench-stable thioamide precursors under mild transition-metal-free, room temperature conditions. This method opens the door for using ground-state-destabilized thioamides for a plethora of C–C bond forming reactions of broad synthetic interest. Considering the recent explosion of interest in amide bond activation methods, we fully expect that thioamides as the closest ‘single-atom’ bioisosteres of amides will be of high value for a broad range of practitioners of chemical synthesis. Further studies on N–C(S) activation are underway and will be reported shortly.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Data availability statements

- The data supporting this article have been included as part of the Supplementary Information.
- Crystallographic data for **3a** has been deposited at the CCDC under 2346234.