A Mild and Chemoselective Thioacylation of Amines Enabled by the Nucleophilic Activation of Elemental Sulfur

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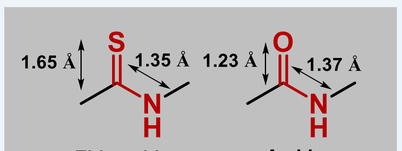
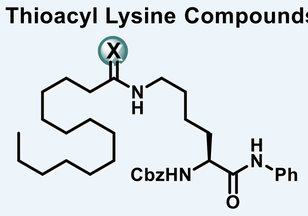
1. Introduction : About Thioamide



- Sulfur is larger than oxygen.
- C=S bond is longer than C=O bond.
- Thioamide has the larger rotational barrier than amide.

• **Thioacyl Lysine Compounds Can Strongly Inhibit the Activity of SIRT2**



	O	S
SIRT1	>200	98
SIRT2	>200	0.028

IC_{50} (μM) values of compounds against SIRT

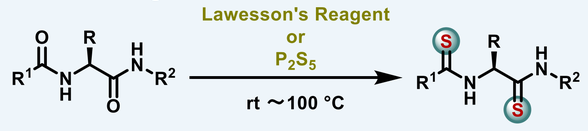
O-S exchange

X = O → X = S

⇨ ***More than 1000-fold increase in anticancer activity***

H. Lin *et al. Cancer Cell.* **2016**, *29*, 297.

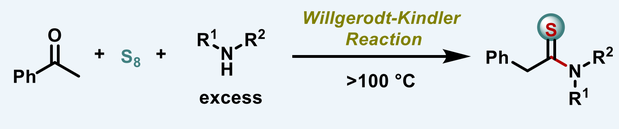
• **O-S exchange Reaction**



✓**Low chemoselectivity**

S. O. Lawesson *et al. Org. Synth.* **1984**, *62*, 158.

• **Willgerodt-Kindler Reaction**

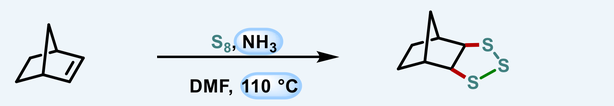


✓**Harsh conditions** ✓**Low functional group tolerance**

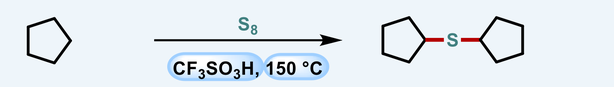
K. Kindler *et al. Liebigs Ann. Chem.* **1923**, *431*, 187.

2. Elemental Sulfur for Organic Synthesis

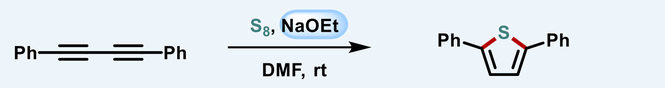
- ***Cyclic molecules S_8***
- ***Stable solid under rt***
- ***Odorless***
- ***Abundant and cheap***
- ***Easy to handle***



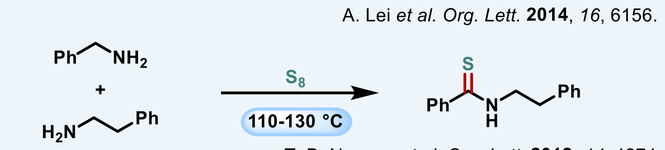
A. N. Kurtz *et al. J. Am. Chem. Soc.* **1969**, *91*, 5415.



G. A. Olah *et al. J. Am. Chem. Soc.* **1990**, *112*, 3697.



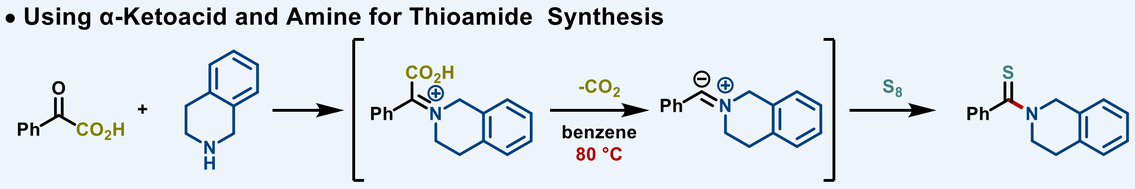
A. Lei *et al. Org. Lett.* **2014**, *16*, 6156.



T. B. Nguyen *et al. Org. Lett.* **2012**, *14*, 4274.

3. Strategy

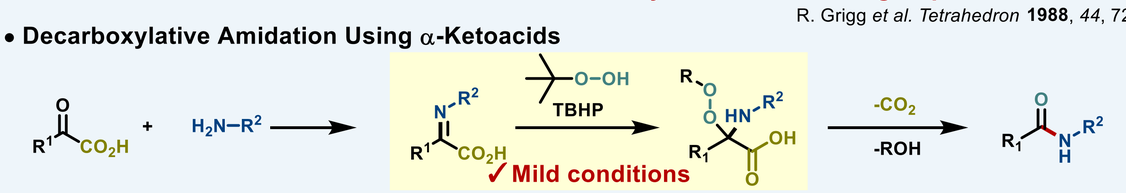
• **Using α-Ketoacid and Amine for Thioamide Synthesis**



✓**Harsh conditions** ✓**Low chemoselectivity** ✓**Low functional group tolerance**

R. Grigg *et al. Tetrahedron* **1988**, *44*, 7271.

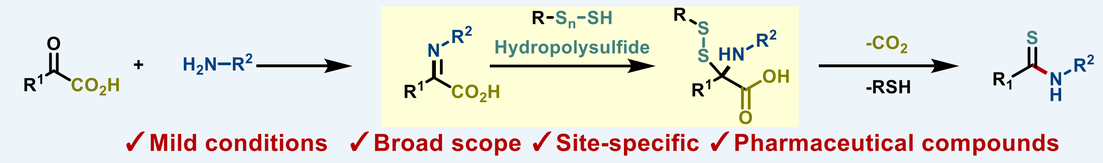
• **Decarboxylative Amidation Using α-Ketoacids**



✓**Mild conditions**

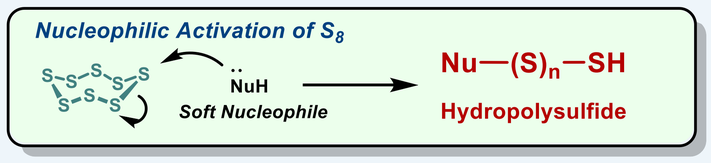
Y. Takemoto *et al. Chem. Eur. J.* **2019**, 25, 15504.

• **Decarboxylative Thioamidation Using α-Ketoacids**

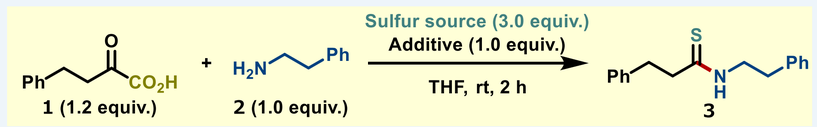


✓**Mild conditions** ✓**Broad scope** ✓**Site-specific** ✓**Pharmaceutical compounds**

Nucleophilic Activation of S_8

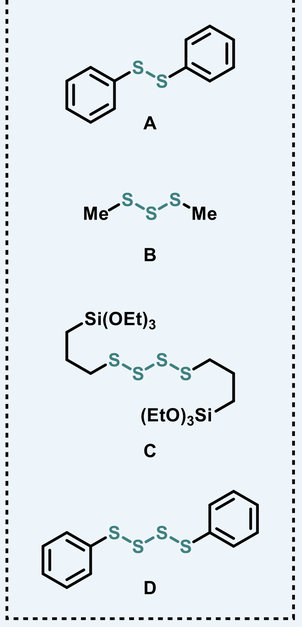


4. Reaction Optimization



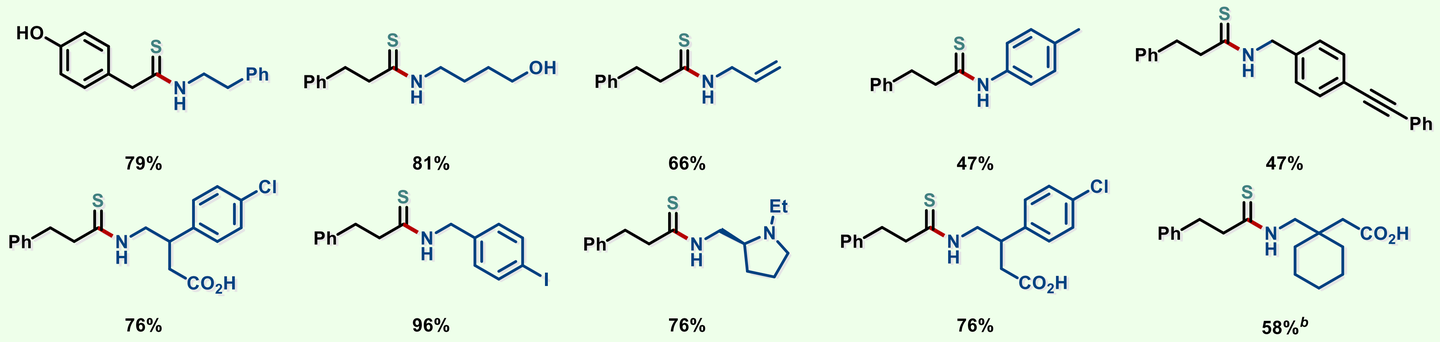
Entry	Sulfur source	Additive	Yield (%)[a]
1	S_8	none	17
2	S_8	Pyridine	12
3	S_8	PCy_3	trace
4	S_8	$^nC_{12}H_{25}SH$	84 (91)[c]
5	S_8	$^nC_{12}H_{25}SH$ (10 mol%)	84
6	S_8	$^nC_{12}H_{25}SH$ (10 equiv.)	21
7	A	$^nC_{12}H_{25}SH$	0
8	B	$^nC_{12}H_{25}SH$	trace
9	C	$^nC_{12}H_{25}SH$	trace
10	D	$^nC_{12}H_{25}SH$	74

[a] The yield was determined by ^1H NMR spectroscopy using dimethyl terephthalate as the internal standard. [b]Equivalent was calculated as the number of S atoms. [c]Isolated yield.

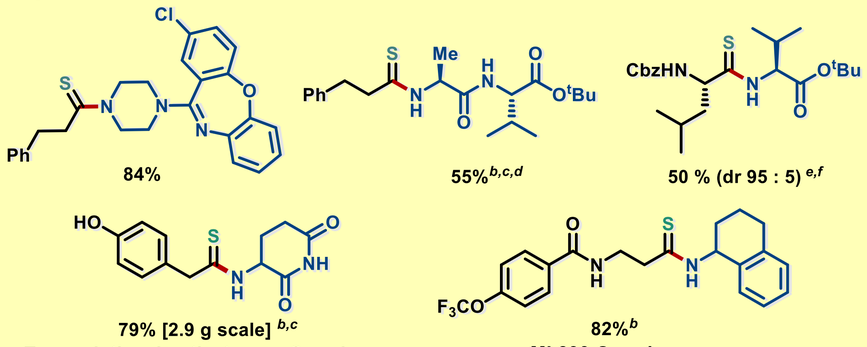


5. Substrate Scope

a) Scope for Functional Group Tolerance



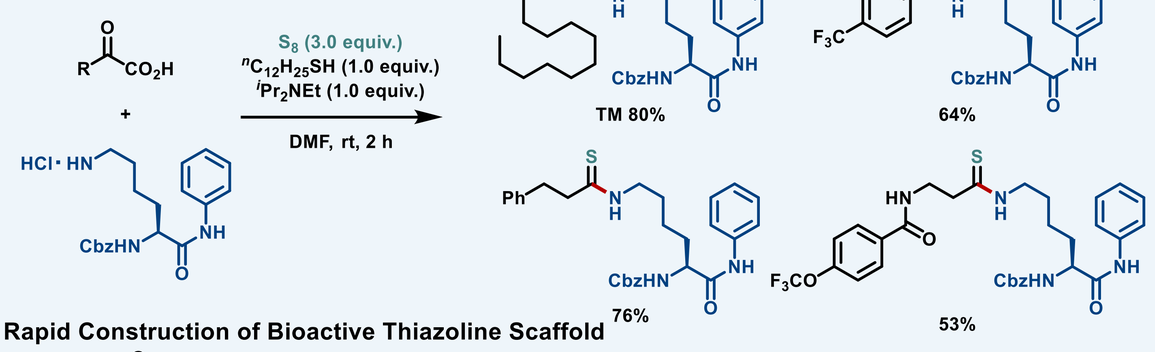
b) Scope of Complex Substrates



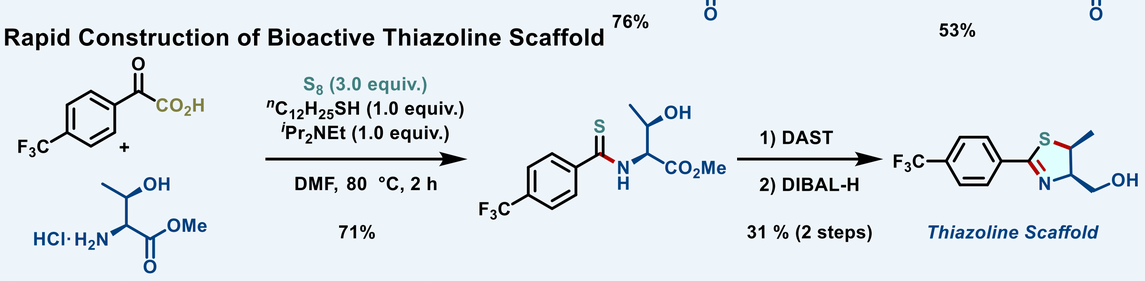
[a]Isolated yields are shown. [b]The reaction was performed in DMF. [c]The reaction was performed at 50 °C. [d]Amine hydrochloride salt (0.10 mmol) and $^iPr_2NEt$ (0.10–0.20 mmol) were used. [e]α-Ketoacid (0.10 mmol), amine (0.12 mol), and 5-^{t}butyl-2-methylbenzenethiol (0.10 mmol) were reacted in DMF/CS_2 (9:1). [f]A solution of the amine and the thiol was added dropwise over 4 h at 80 °C.

6. Application

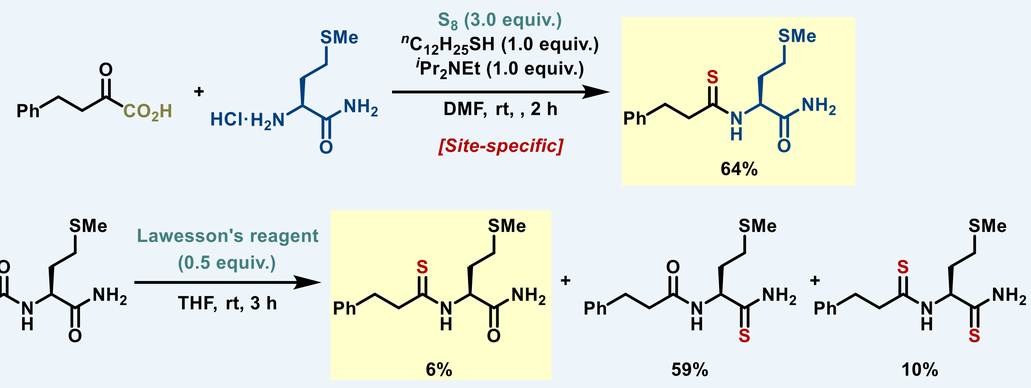
• **Thioacylation for TM Derivatives**



• **Rapid Construction of Bioactive Thiazoline Scaffold**

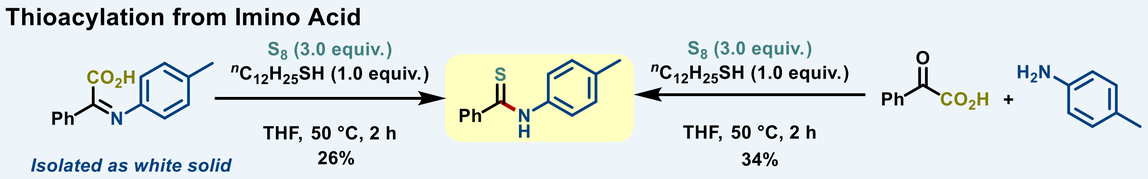


• **Site-specific Thioamide Formation of a Primary Amide-containing Molecule**



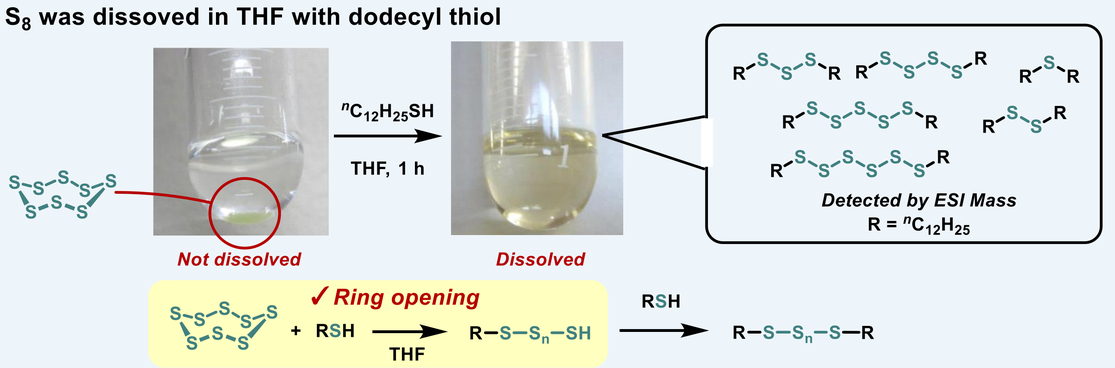
7. Mechanistic Analysis of the Reaction Intermediates

• **Thioacylation from Imino Acid**



✓***Iminoacid is a possible intermediate of this reaction***

• **S_8 was dissoved in THF with dodecyl thiol**



8. Proposed Mechanism