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

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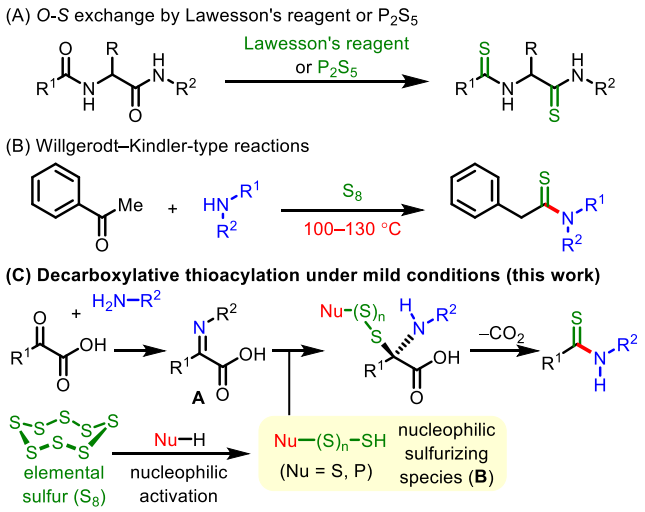
Supporting Information Placeholder

ABSTRACT: A mild and chemoselective method for the thioacylation of amines using α-ketoacids and elemental sulfur has been developed. The key to success for this transformation is the nucleophilic activation of elemental sulfur by thiols such as 1-dodecanethiol. A variety of functional groups, including unprotected hydroxyl, carboxyl, amide, sulfide, and tertiary amine moieties are tolerated under the applied reaction conditions. To demonstrate the advantages of this method compared to conventional *O*-*S* exchange reactions using Lawesson's reagent or P_2S_5, thioamide moieties were introduced site-specifically into biologically active compounds.

Thioamide moieties are commonly encountered in synthetic intermediates. Their synthetic validity is due to their unique reactivity and their ability to serve as building blocks in the synthesis of *S*-containing heterocycles such as thioazoles and thioazolines.[1,2] In addition, thioamides are regarded as bioisosteres of amides that exhibit increased resistance to enzymatic hydrolysis;[3] many articles have described an improved biological activity of pharmaceuticals upon replacing amide with thioamide groups.[4] For instance, thioacyl lysine derivatives possess significantly improved anticancer properties compared to acyl lysines.[4a] Furthermore, Petersson reported that the incorporation of thioamides into peptides provides stability against hydrolysis by proteases without any loss of biological activity.[4b] Although various methods for the synthesis of valuable thioamides have been developed, reliable methods for the site-specific installation of thioamides with good functional-group compatibility remain elusive.[5-7] Conventionally, *O*-*S* exchange reactions in oligoamides are accomplished with Lawesson's reagent or P_2S_5, albeit that this generally results in a mixture of partially converted oligothioamides that may, depending on the reaction conditions, contain unreacted amides (Scheme 1A).[5] While the Willgerodt–Kindler reaction and many variations thereof (Scheme 1B)[6] require only carbonyl compounds, amines, and elemental sulfur, most of these reactions proceed exclusively under relatively harsh conditions and exhibit a severely limited substrate scope. Even though significant effort has been devoted to solving these fundamental problems,[7] the reported methods often suffer from poor site-selectivity and functional-group compatibility. Accordingly, mild and efficient reactions for the chemoselective formation of thioamides with broad functional-group tolerance are highly desirable.

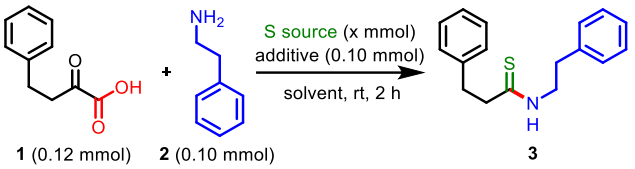
Scheme 1. Decarboxylative thioacylation strategies



Herein, we propose such a chemoselective synthesis of thioamides under mild conditions, inspired by our previous work on the decarboxylative synthesis of amides[8,9] using α-ketoacids, amines, and *t*-butylhydroperoxide (TBHP) via the nucleophilic addition of TBHP to imine intermediate **A**. We envisaged that thioamides could potentially be obtained using a nucleophilic sulfurizing oxidant of the type R-S_n-S-H instead of TBHP (Scheme 1C). Alas, compared to electrophilic sulfurizing reagents, such nucleophilic reagents are scarce.[10] Accordingly, we planned to activate elemental sulfur using nucleophiles (Nu) to generate nucleophilic sulfurizing species **B**, which bears a Nu-S_n-S-H moiety. However, elemental sulfur[11] is generally stable under ambient conditions, and its activation usually requires harsh conditions (acids, bases, or radical initiators

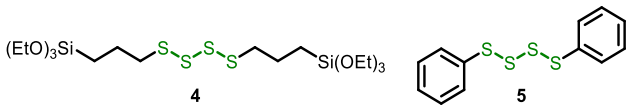
at high temperatures). In order to effectively produce thioamides, we activated elemental sulfur under mild conditions using strong or soft nucleophiles such as thiols or phosphines (Nu = *S*, *P*). Furthermore, chalcogen–chalcogen interactions[12] are expected to aid the nucleophilic activation of elemental sulfur using thiols (Nu = *S*).

Table 1. Optimization of the reaction conditions for the decarboxylative thioacylation



1 (0.12 mmol) **2** (0.10 mmol) **3**

Entry	S source (mmol)	Additive	Solvent	Yield (%)[a]
1	S_8 (0.3)[b]	None	THF	17
2	S_8 (0.3)[b]	None	THF/Py	12
3	S_8 (0.3)[b]	DMAP	THF	12
4	S_8 (0.3)[b]	PCy_3	THF	trace
5	S_8 (0.3)[b]	$Ph_2P(O)H$	THF	0
6	S_8 (0.3)[b]	Cysteine	THF	96
7	S_8 (0.3)[b]	PhSH	THF	quant.
8	S_8 (0.3)[b]	$^nC_{12}H_{25}SH$	THF	84 (91[c])
9[d]	S_8 (0.3)[b]	$^nC_{12}H_{25}SH$	THF	84
10[e]	S_8 (0.3)[b]	$^nC_{12}H_{25}SH$	THF	21
11	S_8 (0.3)[b]	$^nC_{12}H_{25}SH$	DMF	86
12	S_8 (0.3)[b]	$^nC_{12}H_{25}SH$	PhMe	16
13	S_8 (0.3)[b]	$^nC_{12}H_{25}SH$	CH_2Cl_2	23
14	**4** (0.1)	$^nC_{12}H_{25}SH$	THF	trace
15	**5** (0.1)	$^nC_{12}H_{25}SH$	THF	74



4 **5**

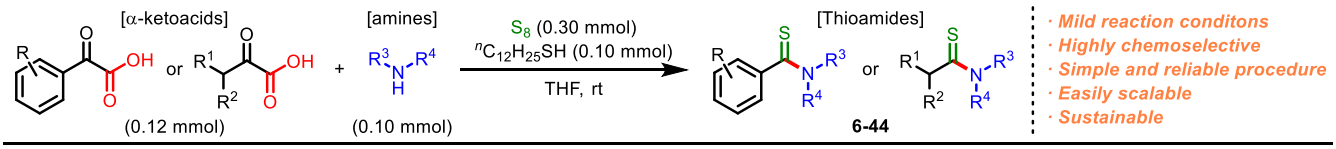
[a]The yield was determined by ^1H NMR spectroscopy using dimethyl terephthalate as the internal standard. [b]The number of mmols was calculated as the number of S atoms. [c]Isolated yield. [d]10 mol% $^nC_{12}H_{25}SH$ was employed. [e]10 equiv. $^nC_{12}H_{25}SH$ was employed.

Initially, the reaction conditions were optimized using α-ketoacid **1**, phenethylamine **2**, and elemental sulfur as substrates (Table 1). When the reaction was carried out in THF without an additive, the obtained yield of the desired product (**3**) was low (entry 1). Subsequently, we examined nucleophilic additives using THF as the solvent (entries 2-8). Although pyridine, DMAP, and PCy_3 did not improve the yield of **3** at room temperature (entries 2-4), the addition of thiols (cysteine, thiophenol, and 1-dodecanethiol ($^nC_{12}H_{25}SH$)) significantly improved the reaction at room temperature and afforded **3** in excellent yield (entries 6-8). Considering price and odor, we chose $^nC_{12}H_{25}SH$ as the optimal additive (entry 8).[13] While the reaction proceeded with as little as 10 mol% $^nC_{12}H_{25}SH$ (entry 9), the thioacylation was hampered by an excess of $^nC_{12}H_{25}SH$ (entry 10); this may indicate that excess thiol causes a fragmentation of S_8 to produce unreactive species. Next, we considered the solvent; DMF produced **3** in high yield (entry 11), whereas less polar solvents such as toluene and dichloromethane produced **3** in merely low yield, even in the presence of thiols (entries 12, 13), which can be explained by the poor solubility of S_8 in these solvents. Finally, we substituted elemental sulfur with several different polysulfides in order to gain further insights on the reactive species in this thioacylation reaction (entries 14, 15). While commercially available dialkyltetrasulfide **4** was not effective for the thioacylation, **3** was produced in 74% yield using diaryltetrasulfide **5**.[14] These results suggest that thiols activate polysulfide S-S bonds and attack the α-sulfur of tetrasulfides to provide reactive RSSSH species.[15]

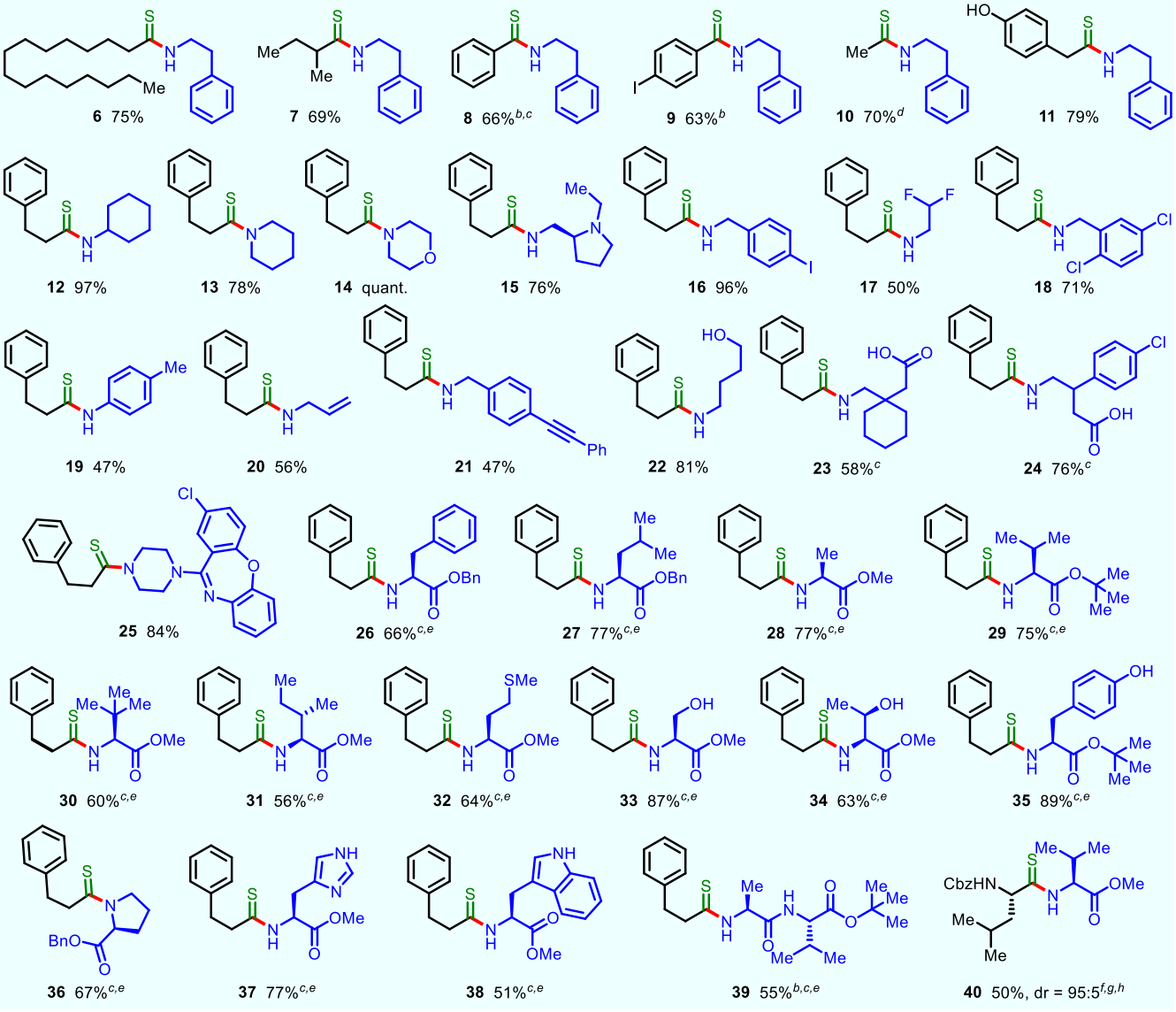
With the optimum reaction conditions in hand, we investigated the substrate scope of the thioamidation reaction between α-ketoacids and amines in order to verify the chemoselectivity and functional-group tolerance (Table 2). α-Ketoacids with linear or branched alkyl substituents provided thioamides **6** and **7** in good yield (Table 2A). In contrast, α-ketoacids derived from benzoic acids produced thioamides **8** and **9** in moderate yield, even when heated, which is presumably due to their lower reactivity. Interestingly, when oxaloacetic acid was used as an acyl source, thioacetylated **10** was obtained in 70% yield via decarboxylation. Our general thioamidation protocol is also applicable to substrates with unprotected OH groups (**11**). Next, we explored the scope with respect to amines. Cyclohexylamine, and secondary cyclic amines, such as piperidine and morpholine, provided thioamides **12-14** in 78-100% yield. In addition, primary amines that bear an additional tertiary amine, iodine, fluorine, or chlorine group(s) provided thioamides **15-18** in good yield. Although the aniline derivatives showed lower nucleophilic activity, *p*-toluidine produced thioanilide **19** in 47% yield. As unsaturated bonds in e.g. alkynes react with elemental sulfur under basic conditions, we also tested alkynes and olefins under the optimized reaction conditions, which provided **20-24** in 47-81% yield. It should be noted here that **20-24** contain unprotected hydroxyl and carboxyl groups, which could potentially be functionalized by coupling and/or substitution reactions. Finally, amoxapine, an antidepressant drug, furnished thioamidated derivative **25** in 84% yield, which offers a method for prodrug synthesis via thioacylation.[16]

To further investigate the functional-group tolerance, we applied various amino-acid derivatives as nucleophiles. Esters of phenylalanine, leucine, and alanine were thioacylated under the optimized conditions to produce **26-28** in 66-77% yield, even when *in-situ*-neutralized amine hydrochloride salts were employed in the reaction. Bulkier amino acids, such as valine, tertiary leucine, and isoleucine motifs, provided **29-31** in 56-75% yield.

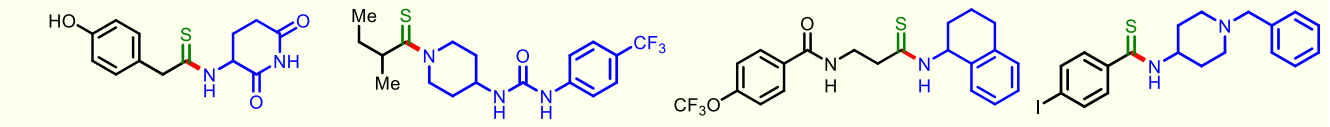
Table 2. Substrate scope of the decarboxylative thioacylation[a]



(A) Scope of α-ketoacids and amines

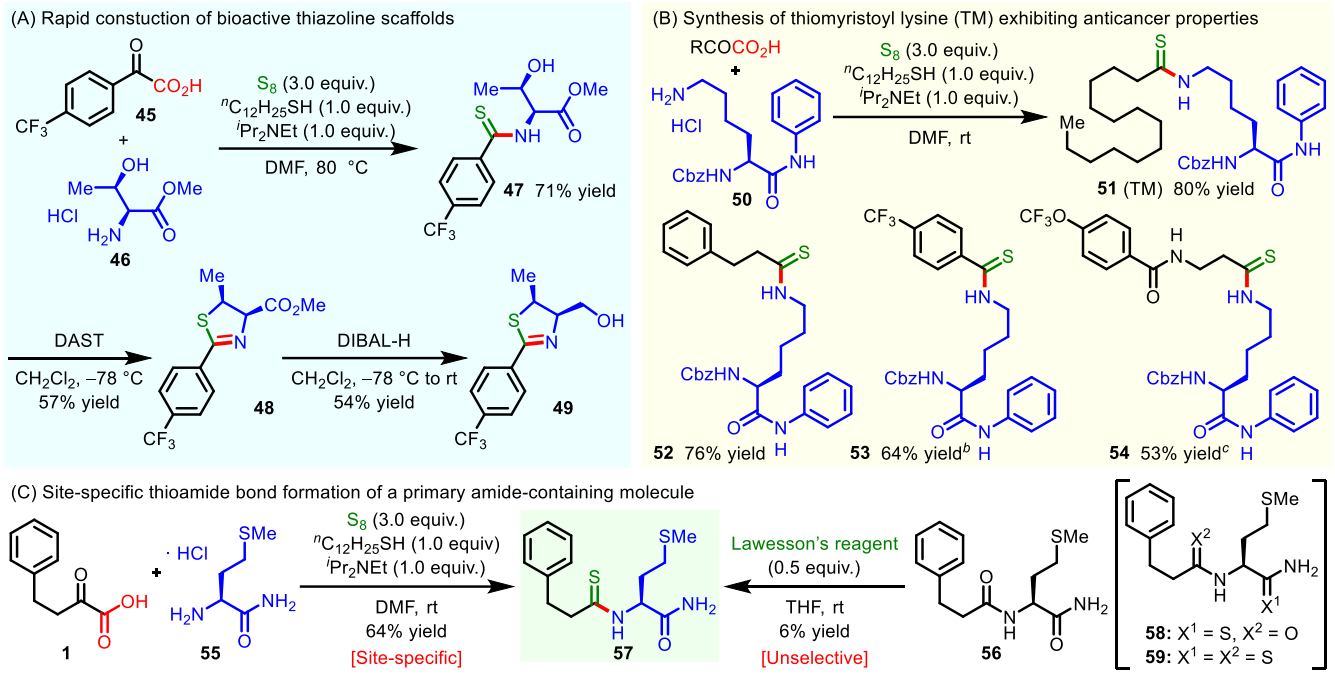


(B) Potential pharmaceutical compounds



[a]Isolated yield. [b]The reaction was performed at 50 °C. [c]The reaction was performed in DMF. [d]Oxaloacetic acid was used as the α-ketoacid. [e]Amine hydrochloride salt (0.10 mmol) and $^{i}Pr_2NEt$ (0.10–0.20 mmol) were used. [f]α-Ketoacid (0.10 mmol), amine (0.12 mol), and 5-tert-butyl-2-methylbenzenethiol (0.10 mmol) were reacted in DMF/CS_2 (9:1). [g]A solution of the amine and the thiol was added dropwise over 4 hours at 80 °C. [h]Dr values were estimated by chiral SFC analysis. [i]The reaction was performed at 80 °C.

Scheme 2. Synthetic applications of the decarboxylative thioacylation of amines[a]



[a]Isolated yield. [b]The reaction was performed at 80 °C. [c]The reaction was performed at 50 °C.

Notably, methionine derivative **32** was obtained in 64% yield without oxidation of the sulfide moiety. In addition, this reaction was applicable to amino acids with unprotected hydroxyl groups (serine, threonine, and tyrosine) to produce thioamides **33**-**35** in good yield. Proline, *N*-unprotected histidine, tryptophan, and dipeptide derivatives furnished thioacylated **36**-**39** in 51-77% yield. Moreover, the thioacylation using an α-ketoacid derived from Cbz-leucine enabled the rapid preparation of peptide thioamide **40**.

Subsequently, we applied this method to synthesize thioamide analogues of pharmaceutical compounds that contain amide groups (Table 2B). A transcriptional antiestrogen[17] *S*-analogue (**41**), an analgesic[18] *S*-analogue (**42**), a human dihydroorotate dehydrogenase inhibitor[19] analogue (**43**), and a selective σ1 agonist[20] analogue (**44**) were obtained in 40-82% yield. Notably, our thioamidation protocol is highly reliable and scalable; for example, **41** could be produced on the gram scale (79% yield, 2.9 g) without the need for any special operational requirements or safety measures.

To demonstrate its synthetic utility, we applied this chemoselective thioacylation reaction to the synthesis of several biologically active compounds (Scheme 2A and 2B). Thiazoline scaffolds with an aromatic ring at the C-2 position are common in various biologically active compounds, including natural products such as pulicatins[21] and the highly potent human peroxisome proliferator-activated receptor-δ agonist.[22] The decarboxylative thioacylation between **45** and threonine derivative **46** furnished thioamide **47** in 71% yield, which was directly converted into thiazoline **49** after treatment with *N*,*N*-diethylaminosulfur trifluoride (DAST), followed by reduction with DIBAL-H (Scheme 2A). Furthermore, the synthesis of thioacylated lysine compounds, which exhibit anticancer properties, was also accomplished using this thioacylation (Scheme 2B).[4a,d] Under the optimized conditions, the amine moiety of a lysine residue was thioacylated using an α-ketoacid derived from myristic acid to obtain thiomyristoyl lysine (TM) compound **51** in 80% yield. The synthesis of thioamide analogues **52**-**54** with different thioacyl groups was straightforward, as various α-ketoacids are commercially available or easily prepared.[23] Finally, we wanted to demonstrate the synthetic advantages of our decarboxylative thioacylation compared to conventional *O*-*S* exchange reactions (Scheme 2C). The decarboxylative thioamidation between **1** and **55** produced thioamide **57** in 64% yield, while the *O*-*S* exchange reaction of **56** using Lawesson's reagent resulted in a mixture of **57**-**59** (mono- or di-thioamides), which is due to the similar reactivity of the amides. These results strongly indicate that this decarboxylative thioacylation strategy is a powerful tool for the selective introduction of a thioamide moiety into molecules that contain several amide bonds.

In conclusion, we have developed a mild and highly chemoselective method for the thioacylation of amines with α-ketoacids. The key to this methodology is the efficient activation of elemental sulfur under mild conditions by thiols. These conditions tolerate a wide variety of functional groups that include unprotected alcohols, phenols, unsaturated bonds, and carboxylic acids. We believe that a site-selective introduction of thioamide moieties into biologically active compounds, including peptides and proteins, will promote structure–activity-relationship and

drug-discovery studies. Studies of this nature are currently in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website.
Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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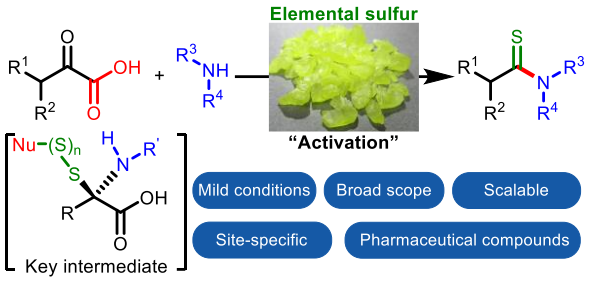

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