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Potassium Thioacids Mediated Selective Amide and Peptide Constructions Enabled by Visible Light Photoredox Catalysis

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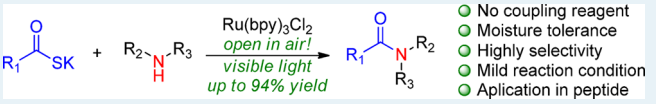
Supporting Information

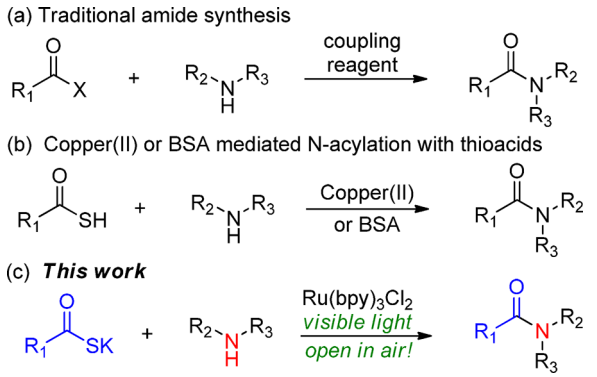
ABSTRACT: A remarkable visible-light-promoted photoredox catalytic methodology involved with amines and eco-friendly potassium thioacids for amide formation was uncovered. This approach can mimic the natural coenzyme acetyl-CoA to selectively acylate amines without affecting other functional groups such as alcohols, phenols, esters, among others. The developed strategy may hold great potential for a comprehensive display of biologically interesting peptide synthesis and amino acid modification through a diacyl disulfide intermediate.



KEYWORDS: *photoredox catalysis, amide formation, potassium thioacids, visible light, peptide synthesis, ruthenium*

Amide motifs are one of the most ubiquitous and intriguing functional groups in the repertoire of organic chemistry, forming the basic building blocks of various biologically meaningful natural products, pharmaceuticals, and agrochemicals.[1] More importantly, they play a pivotal role in natural peptides of biological systems.[2] Due to the significant utilities of such structural motifs, a renaissance was stimulated in exploring mild protocols toward their facile preparations.[1a,3,4] The major issue clouding these significant advances, however, was that these reactions were still restricted to conventional carboxylic acid (or their derivatives) and amines in the presence of coupling reagents, which casts a shadow on resisting moisture sensitivity (Scheme 1a). As a response to these challenges, thioacid-mediated amide formation has emerged as an alternative strategy, thereby improving the overall potential of amide formation.[5,6] Nevertheless, these protocols usually necessitated acidic copper catalysts and pungent thioacids (Scheme 1b). In this regard, the discovery of novel, eco-friendly acylation reagents as well as a green, convenient protocol is still deemed worthy of pursuit.

Scheme 1. Synthetic Approaches to Amide Formation



Photoredox catalysis enabled by green visible light has emerged as a powerful synthetic technology in recent years, providing blueprints for a wide range of synthetically attractive chemical transformations thwarted by orthodox synthetic approaches.[7,8] An array of thiol radical cases,[9] especially its behavior upon visible light photocatalysis,[10] caught our attention during a literature research. At this point, we anticipated that the activation of eco-friendly thioacid salt by visible-light-enabled photocatalysis may possibly generate an active intermediate, which can then be used *in situ* as a mild acylating reagent to directly synthesize the industrially important amide and biologically meaningful peptide in the presence of amine. Herein, a novel, efficient amide and peptide formation facilitated by visible light photoredox catalysis is reported (Scheme 1c).

Key to the success of this amide formation was the activation of inert thioacid salt by judicious selection and modification of reaction conditions. Initially, we tested the possibility of amide formation merging the readily monitored aniline **2** and easily oxidized cesium thioacetic acid, catalyzed by visible light

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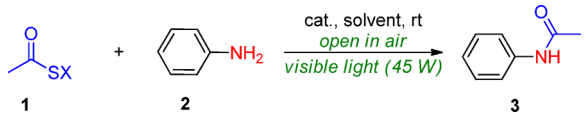
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	cat.	cat. loading	X	1	time	yields[b]
1	ACN	$Ru(bpy)_3Cl_2$	2%	Cs	1.0 equiv	3 h	64%
2	ACN	$Ru(bpy)_3Cl_2$	2%	K	1.0 equiv	3 h	71%
3	ACN	$Ru(bpy)_3Cl_2$	2%	Na	1.0 equiv	3 h	69%
4	ACN	Rose bengal	2%	K	1.0 equiv	3 h	55%
5	ACN	Methyl blue	2%	K	1.0 equiv	3 h	43%
6	ACN	$Ru(bpy)_3Cl_2$	1%	K	1.0 equiv	3 h	54%
7	ACN	$Ru(bpy)_3Cl_2$	5%	K	1.0 equiv	3 h	78%
8	ACN	$Ru(bpy)_3Cl_2$	2%	K	1.5 equiv	3 h	83%
9	ACN	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	3 h	87%
10	THF	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	3 h	<20%
11	DMF	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	9 h	62%
12	DMSO	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	6 h	71%
13	H_2O	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	9 h	55%
14[c]	ACN	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	3 h	<10%
15[d]	ACN	$Ru(bpy)_3Cl_2$	2%	K	2.0 equiv	3 h	0%

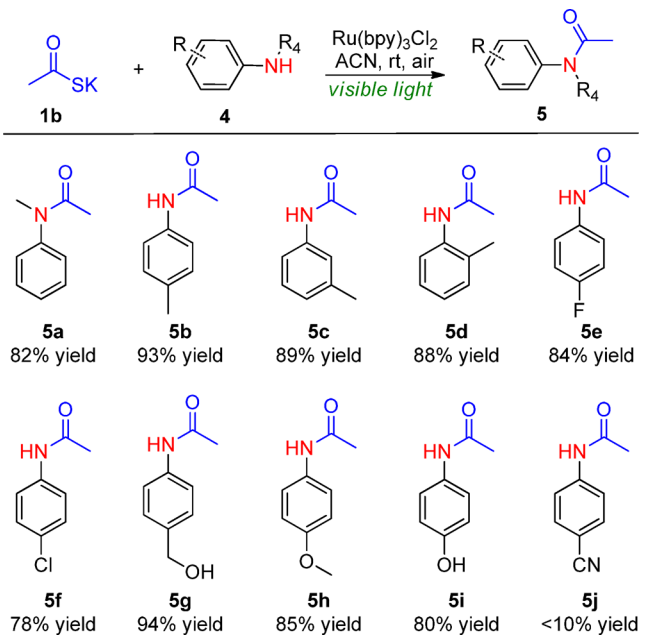
[a]Conditions: **1** (1.0 mmol), aniline **2** (0.5 mmol), cat. (2%), ACN (5.0 mL), rt, 3 h. [b]Isolated yields were reported. [c]The reaction was performed under darkness. [d]**1** was absent.

photosensitizer $Ru(bpy)_3Cl_2$.[10,11] After exposure to a 45 W household bulb light for 3 h, the two substrates were serendipitously converted to amide product **3** in moderate efficiency (64% yield with a trace amount of aniline **2**). In an attempt to improve the yield of this reaction, the contributing factors such as solvents, thioacid salts, substrate loadings, and catalysts[12] that could facilitate this transformation were optimized (Table 1). As a result, the thioacid salts and substrate loadings were proved to be fairly significant during this transformation. Compared with reaction yields caused by diverse thioacetic acid salts, the potassium one ranked the highest yield (71%), whereas cesium and sodium thioacetic acid salts gave 64% and 69% yield, respectively. This result might be attributed to the suitable oxidation activity and weaker basicity of potassium thioacetic acid.[13] Moreover, under otherwise identical conditions, a simple switch of the potassium thioacetic acid loading to two equivalents made the yield dramatically increase to greater than 85%. Although increasing Ru catalyst to 5 mol % somehow improved the yield, we still decided to employ 2 mol % in the following reactions so as to maintain an economical protocol.

Having established the standard reaction condition, we began to assess the substrate scope and versatility of this methodology. As shown in Scheme 2, upon exposure of structurally variable aromatic aniline derivatives **4** to the standard condition, the anticipated aromatic amide products **5a**−**5i** were isolated in a highly efficient manner, with the yield ranging from 78% to 94%.

Notably, steric hindrance of substituents on the aromatic anilines **4** showed little effect on the reactivity, and all the corresponding products **5a**−**5d** were generated in more than 80% yields (Scheme 2). Among which, **5a** gave slightly lower yield possibly due to its strong volatility.[14] Of equal importance to widen the substrate scope was the installation of substituents with different electronic features on the aryl rings (**4d**−**4j**). Gratifyingly, most of anilines with either electron-withdrawing or electron-donating substituents turned out to be convertible, although **4j** with a strong electron-withdrawing group displayed

Scheme 2. Surveying the Scope of Aromatic Aniline Substrates[a]



[a]Conditions: **1b** (1.0 mmol), aniline **4** (0.5 mmol), $Ru(bpy)_3Cl_2$ (2% mmol), ACN (5.0 mL), rt, 1−3 h. Yields of isolated products.

low reactivity. Furthermore, superior selectivity toward acylation of amine motif to free hydroxyl group was also clarified in the case of **4g** and **4i**, with a potential tricky benzylic hydroxyl group and a phenolic one, respectively; this excellent selectivity would constitute the forefront of a mild, green synthetic prowess for amide formation.

Pressing forward, a range of aliphatic primary and secondary amines **6** were subjected to the reaction condition, all successfully accessing the corresponding amide products **7a**−**7j** in moderate to excellent yields (66%−91%) (Scheme 3). It

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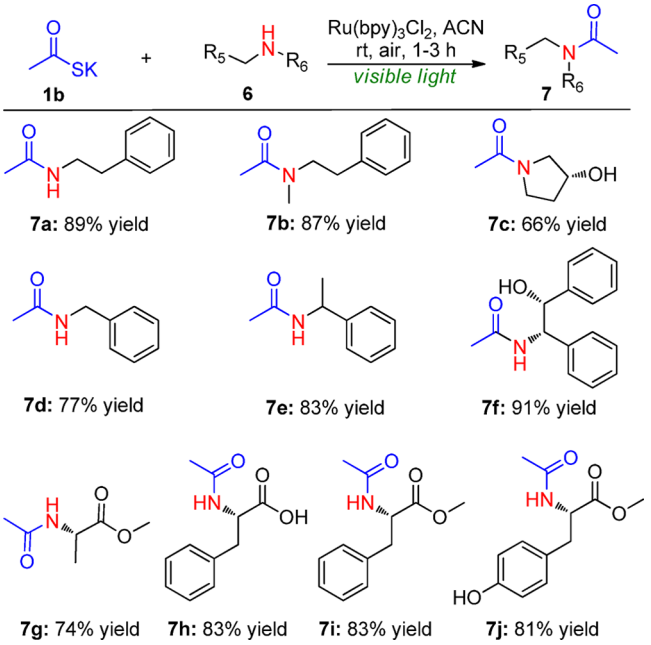
Scheme 3. Surveying the Scope of Aliphatic Amine Substrates[a]



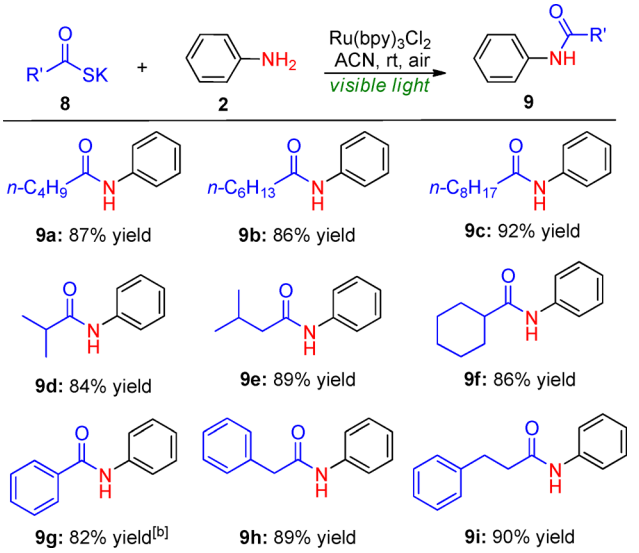
[a]Conditions: **1b** (1.0 mmol), amine **6** (0.5 mmol), $Ru(bpy)_3Cl_2$ (2% mmol), ACN (5 0.0 mL), rt, 1−3 h. Yields of isolated products.

was worth mentioning that substrates **6d**−**6f** with active sp^3 C−H bonds adjacent to a nitrogen atom, which possessed the likelihood to generate structurally robust imine or radical intermediates under visible light photoredox condition,[15] showed no notable loss in the reactivity and selectivity. Up to this point, the versatility of this protocol for the synthesis of biologically important N-acylated natural amino acid derivatives **7g**−**7j** was also evaluated. A collection of formidable substrates, amino alcohols **6c** and **6f**, amino acid **6h**, amino esters **6g** and **6i**,**6j**, as well as amino phenol **6j**, consistently had excellent performance on this reaction. Therefore, this insightful approach may serve as a surrogate to coenzyme acetyl-CoA in terms of mimicking its natural behavior to specifically form amide bonds without affecting other functional groups.[16]

To further extend the scope of this protocol, various thioacids[17] were also examined (Scheme 4) with the reaction conditions slightly modified to the involvement of potassium carbonate, in situ generating the corresponding potassium thioacid **8**. As a result of this endeavor, this transformation tended to smoothly provide the corresponding amide products **9a**−**9c** in better yield when elongating the aliphatic chain appended to potassium thioacid, which might be the result from volatilization hurdles of products. One should also realize that the designed strategy with steric-hindered potassium thioacids **8d**−**8f** also worked remarkably well, suggesting an extremely wide substrate scope. The power of this methodology was also appropriately demonstrated where exposure thiobenzoic acid **8g** or thioacids containing a phenyl group **8h**,**8i** to the standard condition smoothly mediated the formation of N-acylated products **9g**−**9i** in excellent yields. As for the reaction time, almost all the aforementioned reactions could be completed within 3 h, which showed rather satisfying reaction efficiency.

Having executed a novel and efficient synthesis of amide, the stage was now set to begin exploration of its synthetic

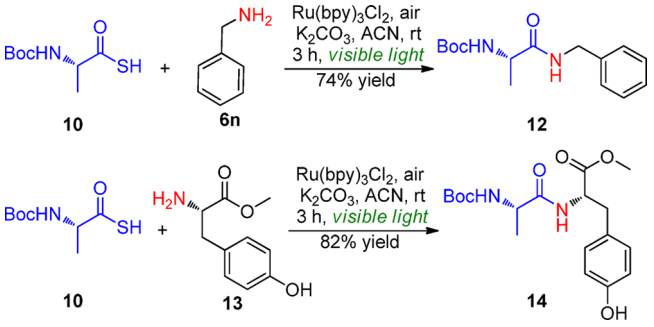
Scheme 4. Surveying the Scope of Potassium Thioacid Substrates[a]



[a]Conditions: **8** (1.0 mmol), aniline **2** (0.5 mmol), $Ru(bpy)_3Cl_2$ (2% mmol), ACN (5.0 mL), rt, 1−3 h. Yields of isolated products. [b]Six h.

application through straightforward synthesis of some pharmaceutically meaningful amino acid or peptide derivatives. As shown in Scheme 5, under the established conditions, the

Scheme 5. Application in Amino Acid Modification and Peptide Synthesis



thioalanine **10**[18] could be smoothly converted to **12** and **14** in 74% and 82% isolated yields in the presence of benzyl amine **6n** and amino ester **13**, respectively. This representative elaboration opened up new vistas in amino acid modification as well as direct peptide synthesis.[19]

Subsequently, mechanistic experiments were conducted to shed light on the potential reaction pathways, as summarized in Scheme 6. With the easily monitored thiobenzoic acid **8g** and aniline **2** as the model substrates, the reaction proceeded smoothly by using the conventional organic photosensitizer rose bengal instead of $Ru(bpy)_3Cl_2$. However, the absence of $Ru(bpy)_3Cl_2$ or rose bengal would result in almost complete inhibition, which strongly implied a visible-light-mediated photoredox process. In order to gain a deep insight into the course of the reaction associated with the isolation of active intermediate, upon exposure of thiobenzoic acid **8g** to potassium carbonate in ACN under the visible light irradiation for 2 h, an instructive disulfide intermediate **15** was obtained in almost 72% yield (brsm), which was fully characterized by

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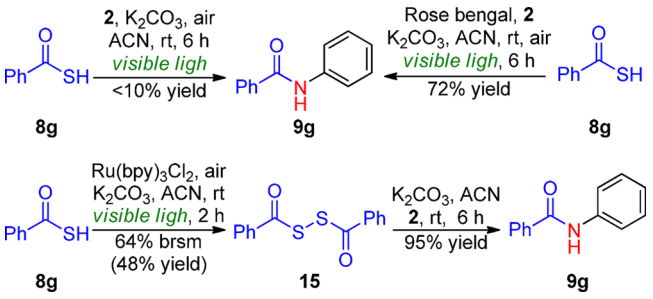
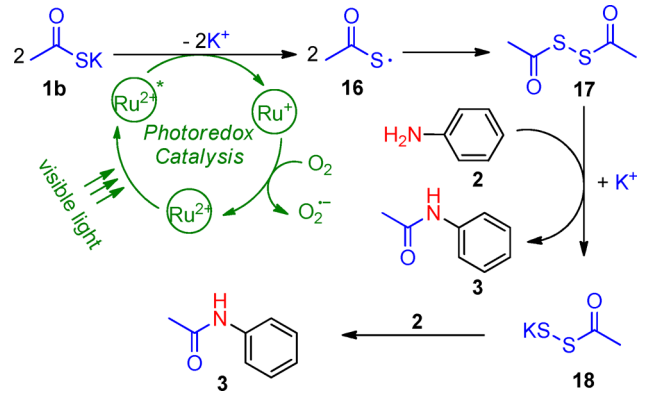
Scheme 6. Experimental Probes on Reaction Mechanism



NMR analysis.[6] Treatment of the freshly generated disulfide **15** with aniline **2** furnished the corresponding amide product **9g** in a highly effective manner.

It is clear that successful trapping of disulfide **15** would bolster a visible-light-mediated photoredox reaction sequence as shown in Scheme 7. Initially, photoexcitation of the Ru^{2+}

Scheme 7. Proposed Mechanism



catalyst by visible-light-generated excited Ru^{2+}*, which was subsequently reduced to Ru^{1+} by the electron-rich thioacetic anion. The involvement of oxygen, converting Ru^{1+} back to Ru^{2+}, cyclized the whole catalytic process. This single-electron transfer (SET) resulted in the generation of thioacetic acid radical **16**, which was transformed to the key intermediate **17** by diradical coupling reaction and then induced the simultaneous amid formation with aniline **2** to afford the desirable amide **3**. The intermediate **18** could further generate amide **3** through aminolysis.[20] As a final note, the aminolysis of **17** was possibly the rate-determining step because of the obvious observation of diacyl disulfide **17** during the reaction process.

In summary, the developed visible-light-promoted photoredox catalytic amide formation was a beautiful case study of judicious selection of a novel acylating reagent, leading to the employment of unconventional eco-friendly potassium thioacid that had greatly expanded our understanding in the realm of amide chemistry. This event was also reminiscent of the natural coenzyme acetyl-CoA to selectively acylate amine motif with other functional groups such as alcohols, phenols, and esters intact. The wide utility and enormous potential of this strategy were reflected in terms of its access to amino acid modification, direct peptide synthesis, as well as the observation of synthetically robust diacyl disulfide. Thus, new ground for amide bond formation in the repertoire of chemistry and biology might be paved with the implementation of our developed strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02943.

General experimental procedures, characterization data, ^1H and ^{13}C NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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(13) The strong basicity of salt thioacid may be induced the hydrolysis of the active intermediate.

(14) The evaporation should be operated under reduced pressure at temperature not exceeding 40 °C.

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