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Visible-Light-Mediated C(sp^3)-H Thiocarbonylation for Thiolactam Preparation with Potassium Sulfide

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Dedicated to Professor Qingyun Chen on the occasion of his 90th birthday.

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Summary of main observation and conclusion We report herein a protocol for thiolactam preparation with potassium sulfide via visible-light-mediated C(sp^3)-H thiocarbonylation, in which polysulfide dianions and radical anions generating from potassium sulfide was the key active species. A variety of thiolactam were straightforward established under mild conditions. Moreover, it was successfully applied to structural modification of Tetrahydroberberine.

Background and Originality Content

Thiolactam is a class of non-negligible sulfur-containing molecules on account of their unique thiocarbonyl motif, which is extensively studied in medicinal chemistry for their unique biological activities. Mercaptopurine[1a] with *N*-heterocyclic thiocarbonyl skeleton is a clinically applied antineoplastic drug and Quazepam[1b] with medium-ring thiolactamide structure is a hypnotic drug. Hydroxymethyl thiolactam cyclothialidine[1c] serves as a DNA gyrase inhibitor (Figure 1a). Moreover, thiolactam structural unit plays a vital role as an active functional group in organic chemical transformations, which has been applied for the formation of C-C bond[2] and C=C bond[3] as well as the construction of complex compounds such as jerantinine.[4] However, limited methods have been developed for the synthesis of thiolactam due to the special structure with C=S bond (Figure 1b).[5] The conventional methods scarcely avoid the utilization of Lawesson reagent or its analogues for transforming carbonyl to thiocarbonyl with the defect of low atomic and environment economy, sometimes with high temperature and uneasy separate byproduct.[5a] Accordingly, environmentally friendly process for thiolactam construction is highly desired. Based on our continuous study of organosulfur chemistry[6] especially in thiocarbonyl chemistry,[7] straightforward structural analysis of thiolactam was orientated to the coupling of sulfur source and carbon center activated by adjacent heteroatom. We envisioned that the C=S bond could be formed by means of direct functionalization of double C−H bonds in the participation of inorganic sulfur source, which will be efficient and economical strategy to construct thiolactam from the corresponding cyclic amine derivatives. Recently, visible-light-mediated C(sp^3)-H functionalization of α-amine C–H bond has drawn significant attention in synthetic chemistry community due to the enhancement of sustainable chemistry route.[8] The amine as the electron donor was used to form photogenically produced amine radical cation, which could further afford the corresponding active α-aminoalkyl radical or iminium ion intermediate.[8c] Inspired by these works and combining our previous exploration of trisulfur radical anion ($S_3^{\bullet-}$),[7c,9] we design that cyclic amines containing methylene adjacent to the nitrogen atom could be activated to generate the α-aminoalkyl radical or iminium ion intermediate through visible-light-mediated way, coupling with sulfur radical species to generate the C-S bond. Herein, we described a mild and high atom economy method for preparation of thiolactams with potassium sulfide as inorganic sulfur source through visible-light-mediated C(sp^3)-H thiocarbonylation reaction under the radiation of blue LEDs (Figure 1c).

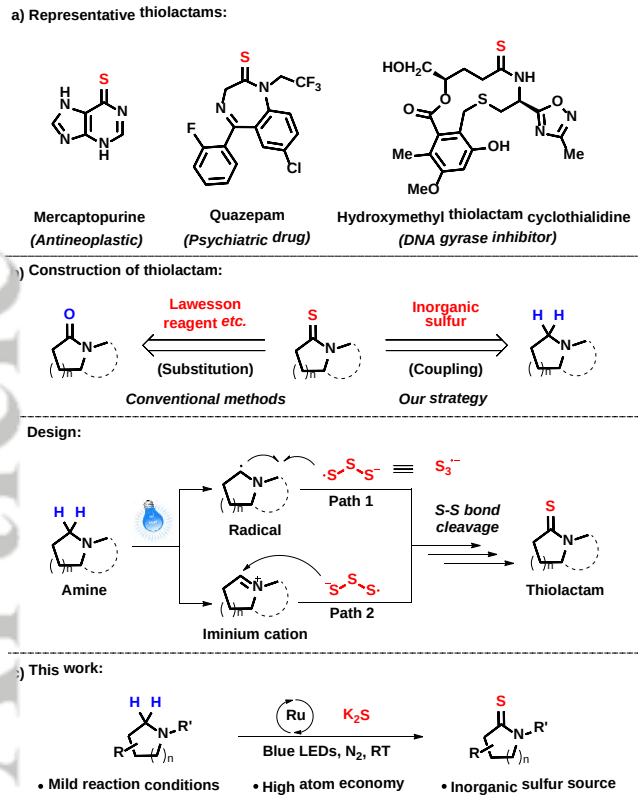
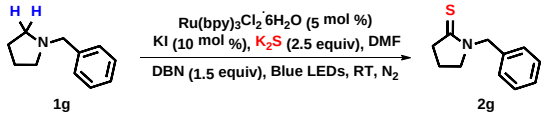


Figure 1 Strategies for thiolactam construction

Results and Discussion

Table 1 Investigation on the establishment of thiolactam [a]



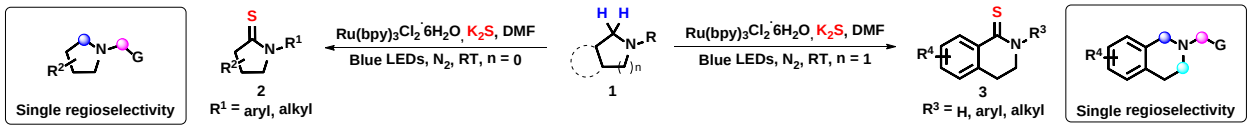
Entry	Change from standard conditions	Yield (%)
1	None	73
2	No $Ru(bpy)_3Cl_2·6H_2O$	ND
3	Air atmosphere	ND
4	In the dark at 70 °C	ND
5	White light (36W) instead of blue LEDs	ND
6	S_8 instead of K_2S	9
7	KSAc instead of K_2S	Trace
8	$Na_2S_2O_3$ instead of K_2S	ND
9[b]	K_2S (1.5 equiv), DMF (0.5 mL)	40
10[b]	K_2S (1.5 equiv), DMF (0.5 mL), no KI	32

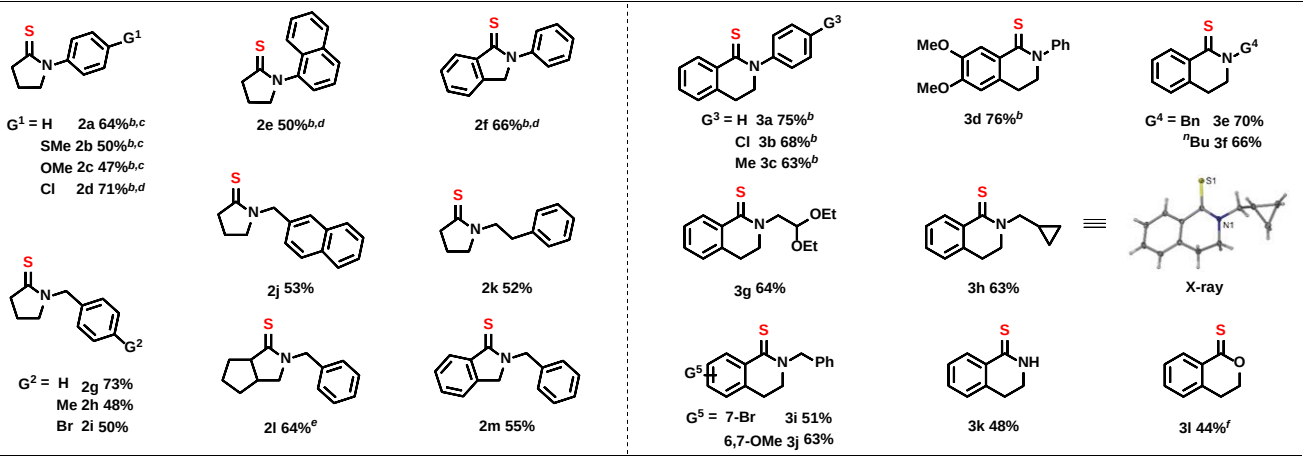
[a] The reaction conditions: **1g** (0.1 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (5 mol %), KI (10 mol %), K_2S (0.25 mmol) and DBN (0.15 mmol), were stirred in DMF (0.25 mL) at RT for 48 h under N_2 atmosphere with blue LEDs radiation. Isolated yields. [b] K_2S (0.15 mmol), 36 h. ND = not detected.

To examine the feasibility of our hypothesis, we selected 1-benzylpyrrolidine **1g** as the model substrate in combination with potassium sulfide as sulfur source. After optimization (see SI for details), the following conditions were employed: $Ru(bpy)_3Cl_2·6H_2O$ as a photocatalyst, 10 mol % of KI as an additive and 1.5 equiv of 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) as base in DMF solvent with the radiation of blue LEDs (3×3 W) under nitrogen atmosphere at room temperature, which is as a model reaction conditions could afford the desired thiocarbonyl product **2g** in 73% yield (Table 1, entry 1). Subsequently, several control experiments were carried out for further understanding of this process. When the photocatalyst $Ru(bpy)_3Cl_2·6H_2O$ was removed in the conditions, the reaction couldn't be in progress (Table 1, entry 2), which revealed that the photosensitizer was indispensable in the reaction. Moreover, it was observed that no expected reaction occurred under air atmosphere, in which perhaps the oxygen-active species in the air contributed to this result[10] (Table 1, entry 3). Meanwhile, considering the effect of thermal reaction, we examined the reaction in the dark at 70 °C, which failed to afford the target product and just recovered large amounts of residual raw material, suggesting that the transformation was indeed driven by light (Table 1, entry 4). Interestingly, if the blue LED irradiation was replaced by white light (36W) in the reaction, no obvious product could be observed, indicating that visible light at a high-energy wavelength was necessary in the process (Table 1, entry 5). Then, we explored several other inorganic sulfur sources to replace potassium sulfide. When elemental sulfur (S_8) was considered as potential sulfur source, only 9% yield of desired product could be isolated, which excluded the possibility that potassium sulfide participated in the reaction process through elemental sulfur form (Table 1, entry 6). If potassium thioacetate (KSAc) or sodium hyposulfite ($Na_2S_2O_3$) was used in the reaction, neither of them could provide desired product effectively (Table 1, entries 7 and 8). Surprisingly, when potassium iodide (KI) was added to the system as an additive, the yield of the product was improved with a certain extent (Table 1, entries 9 and 10).

Based on the optimized conditions, we explored the photocatalytic reactions with a variety of cyclic amines. Firstly, *N*-aryl substituted pyrrolidine derivatives were examined under the corresponding reaction conditions (**2a-f**), which was shown in the left column of Table 2. It could be found that the effect of *para*-substituents on *N*-phenyl ring seem to be obvious. When *N*-phenylpyrrolidine (**2a**) was used as a substrate to afford target

Table 2 Substrate scope for thiocarbonylation of amines [a]



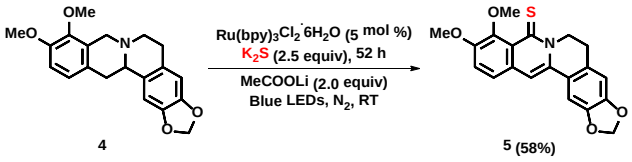


[a]The reaction conditions: blue LEDs radiation, N_2 atmosphere, isolated yields. Method A: **1** (0.1 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (2 or 5 mol %), K_2S (0.25 mmol), KI (10 mol %) and DBN (0.15 mmol), were stirred in DMF (0.25 mL) for 12-48 h. [b]Method B: **1** (0.1 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (2 mol %), K_2S (0.35 mmol), thioacetamide (0.3 mmol) and MeCOOLi (0.3 mmol), were stirred in MeCN (1.0 mL) for 24 h. [c]K_2S (0.15 mmol). [d]48 h. [e]72 h. [f]Method C: **1** (0.2 mmol), $Ru(bpy)_3Cl_2·6H_2O$ (2 mol %), K_2S (0.5 mmol), K_2HPO_4 (0.4 mmol), were stirred in MeCN (2.0 mL) for 16 h.

product in 64% yield, the 1-(4-methoxyphenyl)pyrrolidine (**2b**) or 1-(4-(methylthio)phenyl)pyrrolidine (**2c**) with an electron-donating group provided product in moderate yield. Sterically hindered naphthyl substituted pyrrolidine could also afford the product in moderate yield (**2e**). When *N*-phenyl benzo pyrrolidine was employed (**2f**), the desired product could be isolated in 66% yield. Then, various *N*-alkyl substituted pyrrolidines with an alternative α-amine C–H bond on the alkyl chain were also investigated (**2g-m**) in the standard conditions. The substituents with different electronic effect in the benzyl group were tested (**2g-i**), in which the expected product with electron-withdrawing group (**2h**) or electron-donating group (**2i**) was isolated in significantly decreased yield comparing to the non-substituted benzyl product (**2g**) with 73% yield. Remarkably, no product with thiocarbonylation on C-H bond of *N*-benzyl was detected, suggesting that the process had excellent regioselectivity. When 2-methylnaphthalene (**2j**) or *N*-phenethyl (**2k**) substituted pyrrolidine was selected as the initial material, the reactions could also be carried out effectively and gave their respective products in moderate yields. Subsequently, the bicyclic *N*-benzyl pyrrolidine with five-membered aliphatic ring (**2l**) and 2-benzylisoindoline (**2m**) were explored, in which the corresponding products were obtained in acceptable yields.

Beyond that, tetrahydroisoquinoline as an important hetro ring,[11] was also investigated for thiocarbonylation to afford the related thiolactam through this method (**3a-l**), which was shown in the right column of Table 2. Various *N*-aryl substituted tetrahydroisoquinolines (**3a-d**) with alternative α-amine C–H bond on the same ring were successfully employed under the related reaction conditions and the products with single thiocarbonyl structure could be obtained in good yields. Further, *N*-alkyl substituted tetrahydroisoquinolines (**3e-j**) also were examined and afforded the target products in moderate to good yields along with the formation of a small amount of aromatized byproducts (see SI for details). It is noteworthy that the tetahydroisoquinoline containing an active acetal group (**3g**) and multiple active C-H bonds could be compatible in the reaction and form the product with single regioselectivity. Moreover, high tension cyclopropyl group was also tolerable and the structure of the generated product **3h** was further confirmed through X-ray crystallographic analysis.[12] Meanwhile, the reactions could proceed smoothly using the initial substrates with structural variation on the tetahydroisoquinoline scaffold (**3i-j**). Notably, the unprotected tetahydroisoquinoline bearing an active N-H bond could be transformed into the corresponding thiolactam (**3k**) in moderate yield. Isochroman containing an oxygen atom provide the corresponding product (**3l**) in 44% yield under the photocatalytic conditions, demonstrating the possibility of the visible-light-mediated thiocarbonylation of α-oxygen C–H bond with the strategy.

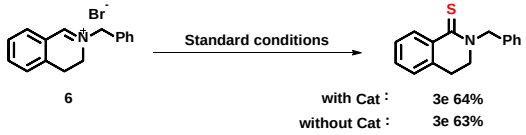
To further explore the potential of this method (Scheme 1), we attempted to apply the method for the structural modification of complicated structure tetrahydroberberine, which as a representative of berberine family alkaloids could be transformed to the related thiocarbonyl derivative **5** in 58% isolated yield along with benzyl oxidation. Here, the main driving forces of oxidation



Scheme 1 Structural modification of Tetrahydroberberine

were high reactivity of benzylic C-H bond and compound aromatization.

To gain the insights into the mechanism, verification experiments were designed (Scheme 2). Considering the possibility of iminium ion as intermediate in the reaction process, 2-benzyl-3,4-dihydroisoquinolinium bromide **6** was prepared as the initial material and subsequently the expected thiolactam (**3e**) was obtained in 64% ^{1}H NMR yield, which implied that the iminium ion intermediate played the key role during this transformation. Moreover, the desired product could be obtained in similar yield as well without photocatalyst, which revealed that the main function of photosensitizer was to achieve the activation of initial amine to afford the corresponding iminium ion intermediate.



Scheme 2 Verification experiment

Furthermore, UV-visible spectra of $Ru(bpy)_3Cl_2·6H_2O$ and K_2S in DMF solution indecated that trisulfur radical anion ($S_3^{\bullet-}$) was readily generated[9d] and the sulfur anion species could coexist with photocatalyst without interaction in non-excited state. Meanwhile, the contrastive fluorescence quenching experiments were conducted to explore that inorganic sulfur species or organic amine species was easier to quench the excited state *Ru(II), in which the obtained sulfur species exhibit stronger quenching effect than amine **1e** according to the related Stern−Volmer plot (see SI for more details).

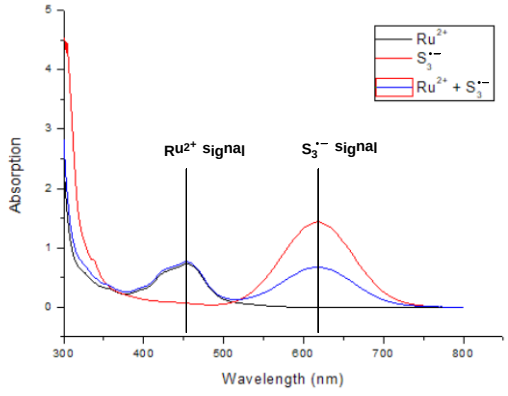


Figure 2. UV-visible spectra: (a) $Ru(bpy)_3Cl_2{\cdot}6H_2O$ in DMF (black line); (b) K_2S in DMF (red line);[9d] (c) $Ru(bpy)_3Cl_2{\cdot}6H_2O$ + K_2S in DMF (blue line).

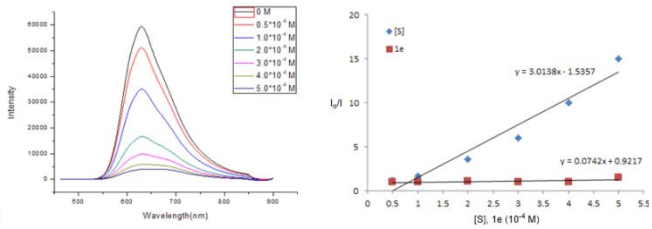
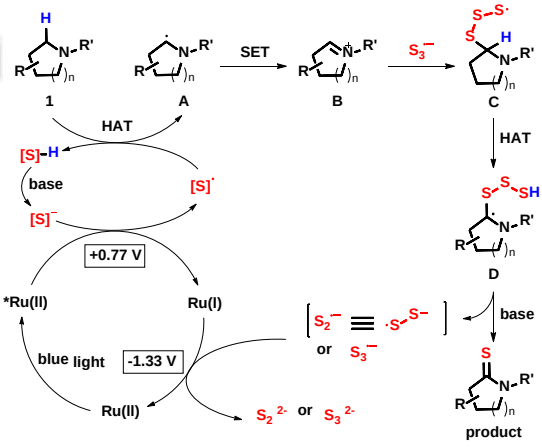


Figure 3. (a) Luminescence quenching of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ with excitation at 628 nm by [S] in DMF (left). The [S] solvent was prepared by using K_2S in DMF. (b)The Stern−Volmer plot (right).

According to all the experimental results, a possible reaction mechanism was depicted in scheme 3. At first, potassium sulfide (K_2S) readily provided trisulfur radical anion ($S_3^{\bullet-}$) in *N*, *N*-dimethylformamide (DMF) solvent,[9d] which was detected through UV-visible spectra. Then, the excited-state *Ru(II) was obtained from the photocatalyst Ru(II) under the irradiation of visible light and was quenched by sulfur anion species $[S]^-$ in the reaction system to achieve the reduced photocatalyst Ru(I) and the corresponding sulfur radical species $[S]^{\bullet}$, which subsequently undergo hydrogen atom transfer (HAT) event with amine **1**, affording α-aminoalkyl radical **A** and sulfhydryl species [S]-H.[13] Then, a facile single electron transfer (SET) process of **A** under weak oxidation conditions formed iminium ion **B**[8e], which could interact with $S_3^{\bullet-}$ and produce intermediate **C** with the establishment of the primary C-S bond. Next, the α-aminoalkyl radical **D** generating from intermediate **C** was obtained through intramolecular hydrogen atom transfer (HAT) process. Finally, the homolysis of S-S bond in the intermediate **D** provided the target product in the presence of base along with the generation of disulfur radical anion ($S_2^{\bullet-}$),[9a,9c] which preferred to get an electron to form a more stable negative ion species (S_2^{2-}). Meanwhile, active $S_3^{\bullet-}$ or $S_2^{\bullet-}$ was considered as the possible electron acceptor and acted as an indispensable oxidant to accomplish the cycle of photocatalysis.



Scheme 3 Proposed mechanism

Conclusions

In summary, we have developed a protocol for preparation of thiolactams with potassium sulfide through visible-light-mediated functionalization of double α-amine C–H bond, even with benzylic hydrogen, in which polysulfide dianions and radical anions generating from potassium sulfide was the key active species to participate in the construction of thiocarbonyl group. A variety of thiolactams were straightforward established by means of the high atom economy strategy under mild conditions. Moreover, this method was successfully applied to structurally complicated modification of tetrahydroberberine. Further study on the thiocarbonylation and related drug discovery is ongoing in our laboratory.

Experimental

The General Synthetic Procedure for Thiolactams

To a solution of *N*-aryl substrate **1** (0.1 mmol, 1.0 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (2 mol %), K_2S (1.5 equiv or 3.5 equiv), MeCOOLi (0.3 mmol, 3.0 equiv) and thioacetamide (0.3 mmol, 3.0 equiv) in MeCN (1.0 mL) were stirred and radiated with blue LEDs (3×3 W) at room temperature for given time under N_2 atmosphere. After the reaction was finished, the solvent was removed under vacuum and purification by column chromatography on silica gel, affording the target product (PE/EA as eluting reagents). PE = petroleum ether, EA = ethyl acetate.

To a solution of *N*-alkyl substrate **1** (0.1 mmol, 1.0 equiv), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (2 mol % or 5 mol %), K_2S (0.25 mmol, 2.5 equiv), KI (10 mol %) and DBN (0.15 mmol, 1.5 equiv) in DMF (0.25 mL) were stirred and radiated with blue LEDs (3×3 W) at room temperature for given time under N_2 atmosphere. After the reaction was finished, the solvent was removed under vacuum and purification by column chromatography on silica gel, affording the target product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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We report herein a protocol for preparation of thiolactams with potassium sulfide through visible-light-mediated C(sp^3)-H thiocarbonylation reaction.

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