RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2022, **12**, 17190

Visible-light-promoted and chlorophyll-catalyzed aerobic desulfurization of thioamides to amides†

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Received 25th March 2022
Accepted 24th May 2022

DOI: 10.1039/d2ra01930b

rsc.li/rsc-advances

A novel method for the metal-free synthesis of amides from thioamides based on visible-light photoredox catalysis and in an air atmosphere is reported. Natural pigment chlorophyll is used as a photosensitizer to generate singlet molecular oxygen $^1O_2$, which is involved in the aerobic desulfurization of thioamides. The protocol provides amides in good yields at room temperature under mild conditions. On the basis of experimental results, a plausible photoredox mechanism is proposed.

Introduction

In synthetic organic chemistry, developing clean and environmentally benign chemical processes using less hazardous catalysts is of great importance and has become a primary goal. In the past decade, visible light photoredox catalysis has become a powerful tool for green organic synthesis due to its sustainability, mild reaction conditions and the potential application of visible light.[1]

In nature, chlorophyll is the most abundant natural visible light photocatalyst.[2] Based on the powerful catalytic ability of chlorophyll, plants use sunlight as the energy source to convert CO_2 and H_2O to sugars. It is the principal photo acceptor in the chloroplasts of most green plants. Chlorophyll is also an ideal and environmentally friendly photosensitizer with porphyrin structures for reactive oxygen species (ROS) generation such as singlet oxygen $^1O_2$. Although reports emerged on the use of singlet oxygen in the synthesis of natural products in the 1980s, chlorophyll was rarely applied in photo driven synthesis. In 2015, Boyer *et al.* utilized the electron transfer mechanism of chlorophyll under light to control radical polymerization.[3] In 2017, He *et al.* reported a chlorophyll-catalyzed synthesis of tetrahydroquinolines mediated by visible light.[4] Inspired by the two precedents of chlorophyll in photosynthesis, we envisaged that it may be possible to use chlorophyll as a highly efficient photosensitizer in visible-light catalysis for organic synthesis or functional group manipulation.

It is well known that thiocarbonyl compounds undergo desulfurization to generate the corresponding carbonyl compounds when treated with stoichiometric oxidants.[5] Molecular oxygen is an ideal environmentally benign oxidant. In 2007, Murai's group reported a copper-catalyzed oxidative desulfurization reaction of thiocarbonyl compounds with molecular oxygen as an oxidant (Fig. 1).[6] In 2016, Mizuno *et al.* found that phosphovanadomolybdic acid could also catalyze the same reaction using molecular oxygen as terminal oxidant (Fig. 1).[7] However, these transformations required reaction temperature at 80 and 60 °C respectively. Afterwards, Yousefi[8] and Frrokhi[9] developed $H_2O_2/TiCl_4$ and $H_2O_2/SOCl_2$ system respectively and lowered the reaction temperature. Nevertheless, above two systems required equivalent $TiCl_4$ or $SOCl_2$ and generated metal salts or chloride wastes. Based on photoredox strategy, Yadav *et al.*[10] found that photo-activated synthetic

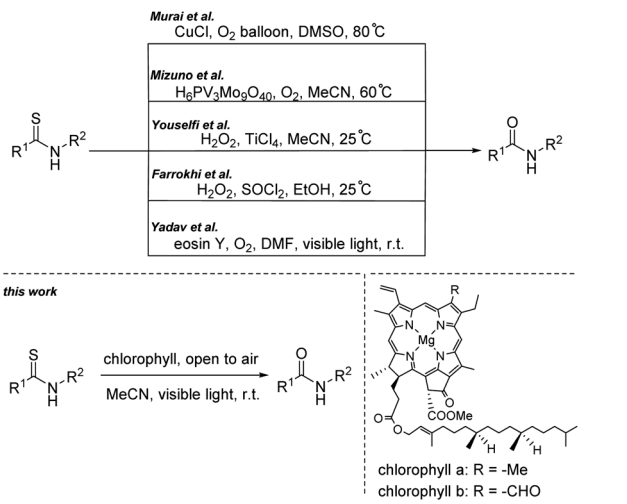

Fig. 1 Desulfurization of benzothioamide.

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† Electronic supplementary information (ESI) available. CCDC 2160655. For ESI and crystallographic data in CIF or other electronic format see https://doi.org/10.1039/d2ra01930b

pigment eosin Y (^{3}EY*) could act as oxidant to achieve the desulfurization of thioamides under aerobic conditions.

In this study, we report that chlorophyll is able to catalyze the desulfurization of thioamides in an air atmosphere under visible light excitation, which provides an example for exploring environmentally friendly and convenient synthetic methodology utilizing chlorophyll and light energy in organic chemistry.

Results and discussion

The natural pigment chlorophyll powder used in this research was purchased from Tokyo Chemical Industry (TCI). This is a mixture powder of chlorophyll, lactose, and dry gum arabic, in which the total chlorophyll is 0.5% (the mass percentage). Initially, a model reaction was carried out with thioamide *N*-phenylbenzothioamide (**1a**). As shown in Table 1, a solution of **1a** in MeCN containing 5 mol% of chlorophyll powder (Fig. 1) was exposed to air atmosphere and irradiated with 455 nm blue LED light at r.t. We were satisfied to found that the reaction gave desired amide **2a** in 84% isolated yield after 8 h (Table 1, entry 1). Prolonging the reaction time to 12 or 24 h (Table 1, entries 2–3) didn't increase the yield of compound **2a** obviously. As control experiments, the reaction was also conducted in darkness or without photosensitizer but only trace of compound **2a** could be detected (Table 1, entries 4–5). In order to check if oxygen is necessary in this desulfurization, the model reaction was carried out in degassed solvent under nitrogen atmosphere, and product **2a** was only obtained in 7% yield (Table 1, entry 6).

It is well-known that chlorophyll can generate singlet oxygen $^1O_2$ upon irradiation in oxygenated solution. In order to verify the existence of singlet oxygen, we did some control experiments under "standard" reaction conditions. When 0.6 mmol (2 equiv.) of 1,4-diazabicyclo[2.2.2]octane (DABCO), which is known as a quencher of singlet oxygen,[11] was added to the model reaction (Table 1, entry 7). The reaction rate was obviously suppressed during the reaction time. Only 5% was obtained in the presence of DABCO after 8 h compared to the yield under "standard" reaction conditions without DABCO (Table 1, entry 7), and no product **2a** was observed within the first 3 h (Fig. 2). The results suggested that singlet oxygen must be involved in the reaction mechanism. As comparison, the

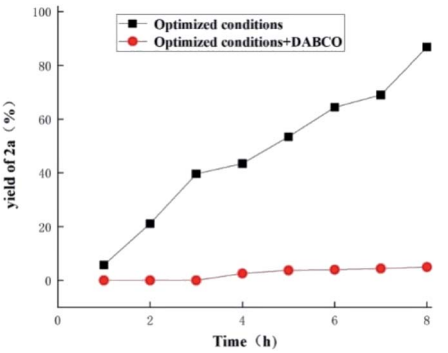
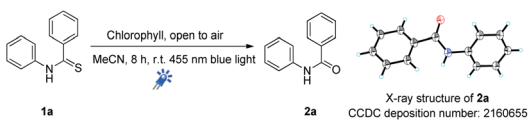


Fig. 2 Influence of DABCO on the model reaction.

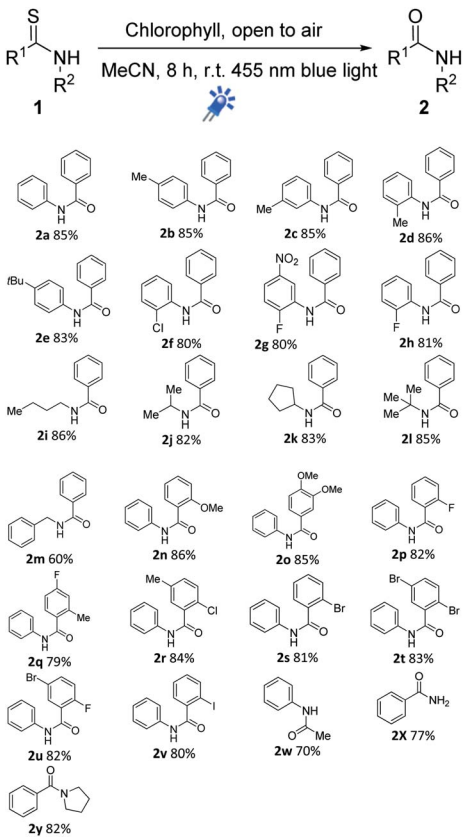
Table 1 Variations from "standard" reaction conditions[a]



Entry	Variation from the optimal conditions	Yields[b]
1	None	84%
2	Prolong reaction time to 12 h	83%
3	Prolong reaction time to 24 h	84%
4	In darkness	Trace
5	Without chlorophyll powder	Trace
6	Under N_2 atmosphere in degassed MeCN	7%
7	Addition of 2.0 equiv. DABCO	5%
8	Addition of 2.0 equiv. of K_2CO_3	54%

[a] "Standard" reaction conditions: a mixture of **1a** (0.3 mmol) and 15 mg of chlorophyll powder (5 mol%) in 3 mL MeCN was stirred and irradiated with 10 W 455 nm blue light-emitting diodes (LED) at r.t. open to air. [b] Yield of the isolated product after silica gel chromatography.

Table 2 Substrate scope of thioamide **1**[a]



[a] Reaction conditions: a mixture of **1** (0.3 mmol) and 15 mg of chlorophyll powder (5 mol%) in 3 mL MeCN was stirred and irradiated with 455 nm blue light-emitting diodes (LED) at r.t. open to air.

addition of inorganic base to the model reaction obviously decreased the reaction efficacy but still delivered target compound **2a** in 54% yield (Table 1, entry 8).

With the optimized condition in hand, we investigated the substrate scope of this photo-activated desulfurization reaction. First, a series of *N*-phenylbenzathioamide with different substituents on the benzene ring of aniline were selected as substrates. As shown in Table 2, alkyl, halogen and electron-withdrawing nitro group didn't have any effect on the desulfurization efficacy (Table 2, compounds **2a**–**2h**). Next, we turned our attention to *N*-alkyl benzothioamide, and were pleased to find that the desulfurization process still underwent highly efficiently (Table 2, compounds **2i**–**2l**). However, the transformation rate of *N*-benzyl benzathioamide slightly decreased (Table 2, compound **2m**). Finally, the effect of acyl groups on the desulfurization reaction was investigated. As illustrated in Table 2, substituents on benzoyl group were tolerant under optimized reaction conditions, giving desired (Table 2, compounds **2n**–**2v**) in good yields. In addition, acetanilide (Table 2, compound **2w**) could be obtained under optimized condition using corresponding benzathioamide as substrate. It should also be noted that even primary and tertiary thioamides were compatible with the present catalytic system, giving corresponding amides **2x** and **2y** in good yields.

To demonstrate the efficiency and applications of this chlorophyll-catalyzed desulfurization reaction, a gram–scale reaction for synthesis of compound **2a** was carried out under "standard" condition. To our delight as shown in Fig. 3, target compound **2a** was obtained in 67% yield. In addition, phenylethanethione **3** and *O*-methyl benzothioate **4** were subjected to this desulfurization reaction, and we were pleased to find that corresponding carbonyl compounds **5** and **6** were obtained in good yields (Fig. 3).

On the basis of our experimental results, we proposed the following plausible reaction mechanism (Fig. 4). Unlike the eosin Y-catalyzed desulfurization of benzathioamide,[10] singlet molecular oxygen is involved in this chlorophyll-catalyzed reaction. Firstly, the chlorophyll is excited from its ground state to its excited state (chlorophyll*) upon irradiation of visible light. The excited state photosensitizer (chlorophyll*)

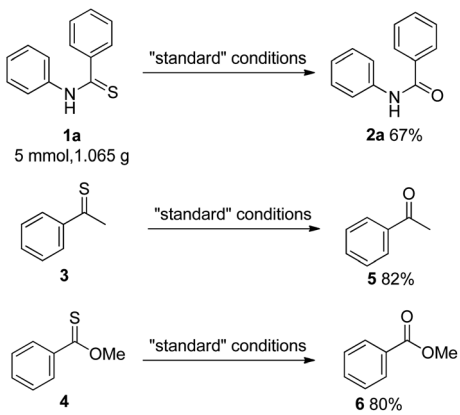


Fig. 3 Further applications of current desulfurization reaction.

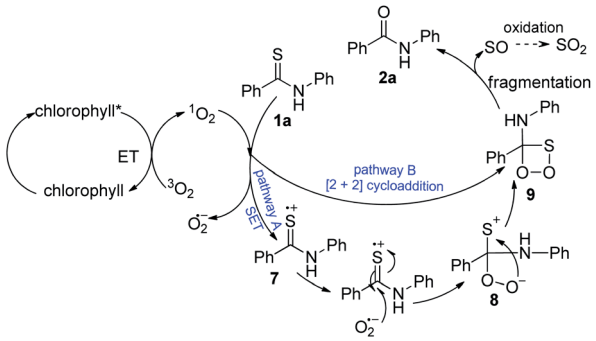


Fig. 4 Possible desulfurization mechanism.

turns the ground-state oxygen $^3O_2$, forming the singlet oxygen $^1O_2$ *via* energy transfer (ET) process.[12] Meanwhile, the excited state of the photosensitizer goes back to the ground state. At this stage, $^1O_2$ can undergo a single-electron transfer (SET) oxidation of benzathioamide **1a** to the thiocarbonyl cation radical **7** (pathway A, Fig. 4). At the same time, singlet oxygen is SET reduced to superoxide anion radicals, which undergoes nucleophilic addition to the C=S double bond of thiocarbonyl cation radical **7**. The addition intermediate **8** cyclizes to four-membered ring intermediates **9**, which finally fragments to product **2a** and sulfur monoxide SO which was further oxidized to SO_2 by singlet oxygen. According to Su's research,[13] O–O bond of $^1O_2$ can undergo a [2 + 2] cycloaddition to the C=S bond of thioamide **1a** directly (pathway B, Fig. 4), forming a four-membered ring intermediate **9**. The C–S bond in intermediate **9** is thus weakened, and the cleavage of the C–S bond leads to product amide **2a** and sulfur monoxide SO which was further oxidized by $^1O_2$ to SO_2.

Conclusions

In summary, a visible-light-promoted and chlorophyll-catalyzed desulfurization of thioamide was developed to access amide. This reaction involves a typical element-transfer process.[14] Compared with previously reported aerobic desulfurization methodology, chlorophyll was able to directly excite ground state oxygen to singlet oxygen $^1O_2$ as oxidant featuring non-toxicity, mild reaction conditions and potential applications of visible light. We believe that the chlorophyll-involved aerobic oxidation system has great application prospect in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was financially supported by Changsha Municipal Natural Science Foundation (No. kq2014064).

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