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Visible light promoted synthesis of *N*-aroylsulfoximines by oxidative C–H acylation of *NH*-sulfoximines

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The visible light-promoted synthesis of *N*-aroylsulfoximines has been accomplished via an oxidative dehydrogenative coupling at room temperature under air without the addition of a photosensitizer, metal catalyst, or base. This process exhibits good functional group tolerance, allows facile isolation and purification, and affords *N*-aroylsulfoximines with high efficiency. The efficiency of the newly developed protocol is described in detail with 27 examples with yields ranging from 80% to 96%. Furthermore, the chirality of the *NH*-sulfoximine is completely maintained in the desired *N*-aroylsulfoximine product (>99% ee).

visible light, aldehyde, sulfoximines, acylation, oxidative dehydrogenative coupling

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1 Introduction

Molecules with sulfoximine structures are of interest because they are widely used in medicine and agriculture (Figure 1) [1]. nAChR agonist I represents a novel insecticide targeting sap-feeding pests with unique resistance and mode-of-action characteristics [2]. The second molecule (II) selectively inhibits COX-2 and hERG [3], and it has been identified as a new agent for insect control due to its nicotinic receptor activity [4]. pan-CDK inhibitor III, which was developed by Bayer (BAY 1000394, now in clinical trials), retains the required high biological activity, improves the solubility, and greatly reduced the carbon anhydrase off-target activity of the drug [5]. Human FXa inhibitor IV was developed to treat thrombotic disease, and it works as a novel replacement of the highly basic amidine group of Betrixaban [6]. In addition, sulfoximines are commonly used as chiral precursors and chiral ligands in asymmetric synthesis [7,8] and in the con-

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With the development of chemical synthesis, alkylations [11], vinylations [12], alkynylations [13], arylations [14,15] and other reactions [16,17] have been reported for the synthesis of various *N*-substituted sulfoximines. *N*-Acylsulfoximines are an important class of sulfoximine derivatives that have found wide applications in both pharmaceutical and synthetic chemistry [18,19].

The traditional syntheses of *N*-acylsulfoximines, important sulfoximine derivatives, mainly rely on the *N*-acylation of *NH*-sulfoximines with acyl chlorides [20,21]. In recent years, some new synthetic methods via oxidative C–N cross-coupling processes [22,23] or oxidative decarboxylative coupling reactions [24] have been developed. Notably, in 2013, Bolm's group [24] developed copper-catalyzed oxidative *N*-acylations of sulfoximines with aldehydes (Scheme 1, eq. (1)). In 2015, the Deng's group [25] developed TBAI/TBHP catalysts, but low yields were achieved (eq. (2)). In 2016, the Guin's group [26] developed an NHC (*N*-heterocyclic carbene) catalytic system with bisquinone as the oxidant, but the

struction of various heterocyclic molecules [9,10].

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complexity of the system made separation and purification more difficult (eq. (3)). Although these synthetic strategies are effective, the use of preactivated coupling agents or transition-metal catalysts is not sufficient for either industrial production or green chemistry.

On the other hand, photochemical synthesis as a new, energy-saving, greener solution and has thus attracted substantial attention from chemists resulting in its rapid development [27–29]. Aldehydes are inexpensive and commercially available. They are useful surrogates for the facile generation of acyl radicals via visible light [30-32]. However, photochemical approaches for preparing *N*-acyl-sulfoximines are rare. Currently, only Bolm *et al.* [18] has developed a photocatalytic approach for preparing *N*-acyl-sulfoximines, and it requires the preparation of highly active Ru catalyst precursors and special substrates (Scheme 1, eq. (4)).

Based on our research on organic sulfur chemistry [33-







35], selective cross couplings [36,37] and oxidative cross couplings [38], we developed a visible light-promoted oxidative cross-coupling reaction for the synthesis of *N*-aroylsulfoximines under mild conditions without a transition-metal catalyst, an exogenous photosensitizer or a base (Scheme 1, eq. (5)).

2 Results and discussion

Initially, we adopted 0.55 mmol of *p*-nitrobenzaldehyde (1a) and 0.5 mmol of *S*-methyl-*S*-phenylsulfoximine (2a) as model substrates and a mixture of TBHP (70% aqueous solution) and $K_2S_2O_8$ as oxidants. These model substrates and the mixed oxidant in CH₃CN under an air atmosphere were irradiated with simulated sunlight (xenon arc lamp) for 12 h, and the reaction afforded **3aa** in 80% yield (Table 1, entry 1).

 Table 1
 Optimization of the reaction conditions^{a)}

We tested different light sources and found that target product **3aa** could also be generated under ultraviolet light, but the yield was substantially lower (Table 1, entry 2). The reaction did not proceed in the dark (entry 3). When we increased the temperature and protected the reaction from light, the yield was less than 10% (entry 4), which means that this is a visible light promoted reaction.

We speculated that this synthesis might occur via a free radical reaction; thus, the selection of an appropriate free radical initiator was of great importance. Therefore, initiators, such as H_2O_2 , *m*-CPBA, di-*t*-butyl peroxide (DTBP), $K_2S_2O_8$ and $(NH_4)_2S_2O_8$, were tested. We found that when the reaction system had only a single initiator, the reaction did not proceed (Table 1, entries 5, 6). However, not all of the mixed initiator systems were successful, for example, $H_2O_2/K_2S_2O_8$ (entry 7). Mixed initiator systems including TBHP and $K_2S_2O_8$, TBHP and $(NH_4)_2S_2O_8$, and DTBP and $K_2S_2O_8$

	HN NOa	/	Î _	0
		additive	N ^S	
	ОНС	solvent, light, T, t		
	1a 2a	-	O ₂ N 3aa	_/
Entry	Oxidant (mole ratio)	Time (h)	Solvent	Yield (%) ^{b)}
1	TBHP/K ₂ S ₂ O ₈ (2:1)	12	CH ₃ CN	80
2 ^{c)}	$TBHP/K_2S_2O_8$ (2:1)	12	CH ₃ CN	57
3^{d}	TBHP/K ₂ S ₂ O ₈ (2:1)	12	CH ₃ CN	Trace
40	$TBHP/K_2S_2O_8$ (2:1)	12	CH ₃ CN	<10
5	$TBHP/K_2S_2O_8$ (0:1)	12	CH ₃ CN	Trace
6	$TBHP/K_2S_2O_8$ (1:0)	12	CH ₃ CN	Trace
7	$H_2O_2/K_2S_2O_8$ (2:1)	12	CH ₃ CN	Trace
8	MCPBA/K ₂ S ₂ O ₈ (2:1)	12	CH ₃ CN	Trace
9	DTBP/K ₂ S ₂ O ₈ (2:1)	12	CH ₃ CN	30
10	TBHP/(NH ₄) ₂ S ₂ O ₈ (2:1)	12	CH ₃ CN	52
11	TBHP/K ₂ S ₂ O ₈ (2:1)	12	THF	42
12	TBHP/K ₂ S ₂ O ₈ (2:1)	12	DMSO	<10
13	TBHP/K ₂ S ₂ O ₈ (2:1)	12	CH_2Cl_2	24
14 ^{f)}	TBHP/K ₂ S ₂ O ₈ (2:0.5)	12	CH ₃ CN	69
15	TBHP/K ₂ S ₂ O ₈ (3:1)	12	CH ₃ CN	85
16	$TBHP/K_2S_2O_8$ (4:1)	12	CH ₃ CN	84
17 ^{g)}	TBHP/K ₂ S ₂ O ₈ (3:1)	12	CH ₃ CN	93
18 ^{h)}	TBHP/K ₂ S ₂ O ₈ (3:1)	12	CH ₃ CN	73
19	TBHP/K ₂ S ₂ O ₈ (3:1)	4	CH ₃ CN	60
20	TBHP/K ₂ S ₂ O ₈ (3:1)	8	CH ₃ CN	80
21	TBHP/K ₂ S ₂ O ₈ (3:1)	16	CH ₃ CN	91
22 ⁱ⁾	TBHP/K ₂ S ₂ O ₈ (3:1)	12	CH ₃ CN	95

a) Reaction conditions: **1a** (0.55 mmol, 1.1 equiv.), **2a** (0.5 mmol, 1.0 equiv.), TBHP (1.0 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.5 mmol, 1.0 equiv.), CH_3CN (1.0 mL), irradiation (visible light, 250 W, xenon arc lamp), rt, air. b) Yields correspond to isolated products. c) Irradiation (UV, 250 W, mercury lamp). d) In the dark. e) In the dark, 80 °C. f) TBHP (1.0 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.25 mmol, 0.5 equiv.). g) **1a** (0.75 mmol, 1.5 equiv.), **2a** (0.5 mmol, 1.0 equiv.). h) **1a** (0.5 mmol, 1.0 equiv.), **2a** (0.55 mmol, 1.1 equiv.). i) 50 °C.

afforded target product 3aa (entries 8-10). Subsequently, the effects of the solvent were investigated. The outcome of the reaction performed in DMSO was the worst, and the outcomes of the reactions conducted in CH₂Cl₂ and THF were also poor (entries 11-13). Fortunately, CH₃CN, which was chosen for our initial experimental conditions, was the best solvent (entry 1). Then, the reactant ratio was screened, and it was found that the best reaction result was obtained when TBHP/K₂S₂O₈ was 3:1 and 1a/2a was 1.5:1.0 (Table 1, entries 14–18). Finally, the reaction time was found to greatly influence the yield. The yield was 60% in 4 h and 80% in 8 h, but the yield did not noticeably change when the reaction time was increased to 16 h (entries 19-21). In addition, the effect of temperature was investigated, and it was found that the vield did not change significantly when the temperature was increased (entry 22). Therefore, room temperature was

Table 2Scope of aldehydes^{a), b)}

selected as the optimal temperature for the reaction system.

With the optimized conditions in hand, the scope of various aldehydes was evaluated (Table 2). 4-Nitrobenzaldehyde (1a) was used as the standard substrate for the reaction, and this substrate afforded the corresponding amide (3aa) in 93% yield. In addition, benzaldehyde without a substituent on the benzene ring gave 3ab in a yield of 92%. Benzaldehydes with various electron-donating substituents, such as *p*-methyl (3ac), *m*-methyl (3ad) and methoxy (3ak), provided the desired products in yields of 89%–94%. Various benzaldehydes with halogen substituents were also efficiently converted to amides (3ae–3aj) in high yields. Substrates with electron-withdrawing groups, such as cyano (3al) and ester groups (3am), also provided high yields of the corresponding products. It seems that the electronic properties of the substituents on the benzaldehyde had no sig-



a) Reaction conditions: aldehyde 1 (0.75 mmol, 1.5 equiv.), S-methyl-S-phenylsulfoximine 2a (0.5 mmol, 1.0 equiv.), TBHP (1.5 mmol, 3.0 equiv.), $K_2S_2O_8(0.5 \text{ mmol}, 1.0 \text{ equiv.})$, CH₃CN (1.0 mL), irradiation (visible light, 250 W, xenon arc lamp), air, rt, 12 h. b) Yields correspond to isolated products.

Table 3 Scope of *N*-aroylated sulfoximines ^{a), b)}



a) Reaction conditions: aldehyde 1 (0.75 mmol, 1.5 equiv.), S-methyl-S-phenylsulfoximine 2a (0.5 mmol, 1.0 equiv.), TBHP (1.5 mmol, 3.0 equiv.), K₂S₂O₈(0.5 mmol, 1.0 equiv.), CH₃CN (1.0 mL), irradiation (visible light, 250 W, xenon arc lamp), air, rt, 12 h. b) Yields correspond to isolated products.

nificant influence on the reaction outcome.

When substrate 1 was 2-naphthalaldehyde, the corresponding amide was generated in 85% yield. Unexpectedly, the yields of the amides from heteroaromatic aldehydes (**3ao** and **3ap**) could reach 84%–86%. In addition, a conjugated system such as cinnamaldehyde (**3aq**) could be converted into the desired product in a good yield.

Next, the scope of the *NH*-sulfoximines was evaluated (Table 3). Various substituents, such as methyl (**3ba**), F (**3bb**), Cl (**3bc**), Br (**3bd**), methoxy (**3bf**) and nitro (**3bh**), on the benzene ring of the *NH*-sulfoximine were well tolerated in the reaction, and the yields of their corresponding products were in the range of 85%–96%. The yields obtained with *S*-methyl-*S*-phenylsulfoximines with a bromo substituent at the *ortho*- or *para*- position of the phenyl ring (**3bd** and **3be**) demonstrate that the position of the substituents on the sulfoximines has a minor effect in this reaction. In addition, bisaryl and bis-alkyl sulfoximines such as iminodiphenyl-sul-

fanone (**3bi**), dibutyl (imino)-sulfanone (**3bj**), and dibenzyl (imino)-sulfanone (**3bk**) are also excellent substrates and provided yields in the range of 80%–92%. Furthermore, a cyclic sulfoximine, *S*,*S*-tetramethylenesulfoximine (**3bl**), was also tolerated in this reaction.

Sulfoximines serve as potential chiral ligands for asymmetric catalysis [7,8], so we synthesized chiral *N*-benzoylated sulfoximines. The reaction of commercially available (R)-S-methyl-S-phenylsulfoximine ((R)-2a, >99% ee) and *p*-nitrobenzaldehyde (1a) and 4-bromobenzaldehyde (1h) afforded (R)-3aa and (R)-3ah with>99% ee in 91% and 87% yields, respectively (Scheme 2, eq. (6)) [21]. The results show that the chirality of the enantiomerically enriched sulfoximine is well preserved in this transformation as no racemization occurred during the reaction. We believe that this strategy will facilitate the development of sulfoximine-type chiral drugs and chiral ligands.

To verify the effectiveness of our synthetic method in

practice, a gram-scale experiment was conducted. With 10 mmol of the corresponding *NH*-sulfoximines as the starting materials, **3aa** and **3ac** were obtained in 87% and 83% yields, respectively, within 12 h. Interestingly, heteroaromatic aldehyde **3ap** gave a good yield after increasing the reaction time to 16 h (Scheme 3, eq. (7)).

To study the mechanism of the reaction, we conducted control experiments (Scheme 4). The above experimental results were obtained in a photochemical instrument using a xenon arc lamp as the light source to simulate sunlight. Here, we conducted a reaction under sunlight alone and found that the yield of the targeted amide reached 84% (eq. (8)).

We further studied whether this reaction involves a free radical. Thus, we added 2.0 equiv. of TEMPO to the reaction system, and after 12 h, no **3aa** was detected. The TEMPO-aldehyde adduct was identified as the major product of this reaction (eq. (9)) [24]. This control experiment verifies that this is a free radical-type reaction.



Scheme 2 The synthesis of chiral *N*-benzoylated sulfoximines.



Scheme 3 Gram-scale synthesis.



To verify if the aldehyde in the reaction is first converted to the carboxylic acid before being further transformed, p-nitrobenzoic acid (5) and S-methyl-S-phenylsulfoximine (2a) were reacted for 12 h under the optimized conditions, but no reaction was observed (eq. (10)). Therefore, the reaction did not follow this pathway.

Based on the above control experiments and related literature reports of photoinduced reactions conducted under visible light [39–41], a free radical reaction mechanism was proposed (Scheme 5). $K_2S_2O_8$ generated sulfate radical anions (SO₄⁻) **6** under visible light [42,43]. TBHP produced *t*-butyloxy radical 7 and hydroxyl radical under the action of visible light or produced peroxy-*t*-butyl radicals **8** under the action of sulfate radical anion (SO₄⁻) **6**. Then, free radicals **7** or **8** reacted with aldehyde **1** to produce *t*-butyl alcohol or *t*-butyl hydrogen peroxide and aldehyde radical **9**, which can be trapped with TEMPO by the experimental verification (eq. 9, Scheme 4), [44,45]. In the assistance of free radicals **7** or **8**, aldehyde radical **9** reacted with *NH*-sulfoximines **2** to afford the amidation product **3** and *t*-butyl alcohol or *t*-butyl hydrogen peroxide [46].

3 Conclusions

We developed the first visible light-promoted synthesis of *N*-acylsulfoximines with TBHP/ $K_2S_2O_8$ as a free radical source. This synthetic method has some notable features, including good functional group tolerance, a broad substrate scope with respect to both sulfoximines and aldehydes, and easy separation and purification of the product. In addition, the reaction does not require a transition-metal catalyst, an exogenous photosensitizer, or a base. Many products of this synthetic method are potential intermediates for medicinal and organic chemistry. Therefore, this synthetic method can



Scheme 5 A plausible mechanism (R[•] is free radical).

be used as a practical alternative to existing methods for the preparation of *N*-acylsulfoximines.

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