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Visible-light promoted dithioacetalization of aldehydes with thiols under aerobic and photocatalyst-free conditions[†]

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A novel photocatalyst-free visible-light-mediated dithioacetalization of aldehydes and thiols has been developed. This protocol is operationally simple, mild and atom-economical, which provides an environmental benign access to dithioacetals at room temperature under aerobic conditions.

Thioacetals are versatile building blocks widely used in the synthesis of bioactive natural products and pharmaceuticals.^{1,2} Moreover, thioacetals serve not only as masked acyl anions³ but also as masked methylene functions⁴ in the construction of C-C bonds. Hence, considerable efforts have been made to prepare thioacetals.⁵ Among the various established approaches, the condensation reaction between thiols and aldehydes or ketones is unarguably the most direct one. However, this type of condensation reaction typically involves the use of strong Brønsted acids,⁶ Lewis acids⁷⁻⁹ or high energy microwave irradiation¹⁰ and UV light irradiation¹¹ to activate the carbonyl group. The harsh reaction conditions not only affect the functional group tolerance but also make the work up and product purification process tedious and difficult. All these disadvantages seriously limited the use of thioacetals in organic synthesis. Accordingly, it is still in great urgency and highly desirable nowadays to find mild, costeffective condensation reaction conditions between aldehydes and thiols to prepare thioacetals.

The sustainable development of human society requires chemists to reduce the environmental impact of chemical industrial process as much as possible which led to the birth of green chemistry. And one of the most important tasks of green chemistry is the development of new environmentally

benign synthesis methods and reaction conditions to replace the original unfriendly ones. Over the past decade, visible-light photo(redox) catalysis has emerged as a vital and powerful platform for the development of novel "green" organic reactions with high synthesis efficiency and functional group tolerance.¹² Very recently, Lei *et al.* reported that the aldehyde activation could be achieved via visible light irradiation via an energy transfer process.¹³ In this context, they described a simple and general approach for acetalization of aldehydes with a catalytic amount of Eosin Y as the optimal photocatalyst at room temperature under low-energy visible light irradiation. Inspired by Lei's work, we speculated that the dithioacetalization reaction of aldehydes and thiols could also be promoted by visible-light irradiation. And due to thiols' weak acidity, stronger nucleophilicity and ease of radical generation by aerobic oxidation, their condensation with aldehydes assisted by visible light irradiation might be more facile and possibly exhibit a different reaction mechanism. So we recently initiated a program towards the direct synthesis of 2-aryl-1,3diathians from aldehydes and 1,3-dithiol assisted by visible light irradiation. Herein, we wish to report a facile and mild protocol for the dithioacetalization reaction of aldehydes under aerobic and photocatalyst-free conditions through a visible light photoredox catalysis way (Scheme 1).

Initially, our investigation started by using commercially available benzaldehyde (1a) and 1,3-propanedithiol (2a) as model substrates in the presence of photocatalysts under the irradiation of blue LED light (Table 1). Since a different mechanism was involved a possible sulphur radical was anticipated to work in the dithioacetalization reaction, and all the reactions were conducted under air. As we expected, when the reaction was performed in the presence of a series of common photocatalysts such as Methylene blue, Rhodamine B, Acid Red 87, Ru(bby)₃Cl₂, and Eosin Y, the desired product (3a) was obtained in high yield in all cases (Table 1, entries 1–5). In entries 2 and 3, a minor side product was also obtained at the same time. It was deduced to be toluene by a later GC-MS analysis of the corresponding crude reaction products which

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Previous works

$$R^{1} H HS - R^{2} \xrightarrow{\text{Brønsted or Lewis acid}} R^{1} SR^{2}$$

This work



Scheme 1 Visible-light-promoted direct synthesis of thioacetals from aldehydes and thiols.

might be the reduction product of 1a by thiol 2a. To our delight, in a subsequent control experiment to show the essence of the photocatalyst (Table 1, entry 6), the condensation reaction of 1a and 2a went smoothly to afford the desired product 3a in 98% yield in the absence of any photocatalyst and no reduction side product was detected at this time. It was then assumed that the slow generation of sulphur radical without the photocatalyst increased the chemoselectivity of this reaction and decreased the amount of reduced side products. So the yield is a little high without the photocatalyst compared to that with the photocatalyst (Table 1, entry 6 vs. 2 or 3). A further control experiment without the photocatalyst and LED light irradiation only recovered the two starting materials (Table 1, entry 7). With the optimized conditions in hand, we sought to examine the scope and generality of the method (Table 2). In general, both electron donating and electron-withdrawing substituent attached aromatic aldehydes provided the desired 2-aryl substituted 1,3dithians in high yields. It should be noted that a wide range of functional groups such as i-Pr (3d), OMe (3b, 3n, 3p), SMe (3c), OH (3m, 3s, 3t), F (3f, 3q, 3r), Cl (3g), Br (3h, 3o-3r, 3u, 3v), I (3i), CN (3k), CF_3 (3j) and CO_2Me (3l) were compatible with

Table 1 Optimization of the reaction conditions^{a,b}

	0 1a	+	SH SH 2a	photocatalyst 6 W blue LEDs MeCN, air, rt	S S 3a
Entry		Photocatalyst			$\operatorname{Yield}^{b}(\%)$
1		Methylene blue			99
2			Rhoda	97	
3			Acid I	93	
4			Ru(bb	99	
5			Eosin	99	
6 ^{<i>c</i>}			_		98
7^d			_		n.d.

^{*a*} Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), photocatalyst (3 mol%) in MeCN (1.5 mL) irradiation using 6 W blue LEDs under air at room temperature for 3 h. ^{*b*} Isolated yield. ^{*c*} Without photocatalyst, 24 h. ^{*d*} Without photocatalyst and LED irradiation, 24 h.



^{*a*} Reaction conditions: **1** (0.5 mmol), **2a** (0.55 mmol) in MeCN (1.5 mL) irradiation using 6 W blue LEDs under air at room temperature for 24 h. ^{*b*} Isolated yield.

this reaction, providing the possibility for further transformation. Neither the electron-rich groups nor electron-poor ones located at the *para* or *ortho* position of the aryl aldehyde had significant deleterious effects (3b-3s). Heteroaryl aldehydes such as 3-bromo-2-furaldehyde (1u), 4-bromo-2-thiophenyl aldehyde (1v) and 1*H*-indole-3-carbaldehyde (1w) were well tolerated under the reaction conditions and readily underwent dithioacetalization reactions to afford the corresponding 1,3dithians.

Next, we turned our attention to explore the reactivity of other aldehydes and ketones in this process. To our delight, aliphatic, α , β -unsaturated aldehydes and cyclohexanone were all good substrates for this visible light promoted dithioacetalization reaction. As shown in Table 3, cyclohexanecarbaldehyde

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^{*a*} Reaction conditions: 4 (0.5 mmol), 2a (0.55 mmol) in MeCN (1.5 mL) irradiation using 6 W blue LEDs under air at room temperature for 24 h. ^{*b*} Isolated yield.

(5c), 3-phenylpropyl aldehyde (5e) and *n*-heptaldehyde (5f) all afforded the desired dithiane products in 94% yields. Even steric hindered aliphatic aldehydes which contained an i-Pr or a t-Bu group at their α -carbons also gave the corresponding products in modest yields (5g and 5h). Nevertheless, this reaction could also be applied to phenylpropiolaldehyde and provided the desired dithiane (5a) in 34% yield. Adkins and Hartung reported that extended conjugation results in a lower reactivity for acetalization.¹⁴ Our experiment results indicated that phenylpropiolaldehyde reacted significantly more slowly than phenylpropyl aldehyde and it was in agreement with their report. In addition, cyclic substituents attached at their α position of the aldehydes did not significantly affect the reaction, furnishing the desired products (5b-5d) in excellent yields. In particular, dithioacetalization of cyclohexanone proceeded smoothly to generate the corresponding product (5i) in 89% yield; however cycloheptanone did not react at all and no 5j was obtained. These results were in agreement with those from the acid-catalyzed acetalization of carbonyl compounds reported by Brown¹⁵ and Djerassi.¹⁶ In both studies it was observed that cycloheptanone reacted more slowly than cyclohexanone.

Finally, various thios were screened for this visible light promoted dithioacetalization reaction. As illustrated in Table 4, 1,2-ethanedithiol was firstly proved to be another suitable sulphur source (7a-7f). 2-Aryl- (7a-7d), 2-thiophenyl- (7e)and aliphatic- (7f) 1,3-dithiolanes were all obtained in modest to high yields. And the commercial available diastereomeric **Table 4** Resultsforvisible-light-induceddithioacetalizationdifferent thiols with diverse aldehydesa,b,d



^{*a*} Reaction conditions: **6** (0.5 mmol), **2** (0.55 mmol) in MeCN (1.5 mL) irradiation using 6 W blue LEDs under air at room temperature for 24–48 h. ^{*b*} Isolated yield. ^{*c*} Overall yield. ^{*d*} The reaction was monitored by TLC.

2,3-butanedithiol also reacted well to give the corresponding 2,4,5-tri-substituted 1,3-dithiolanes (7g-7k) in expedient yields as a mixture of multiple diastereomers in which the 2,4,5-*cis* product was the major ones and its structure was confirmed by NMR spectroscopy data and X-ray single crystallographic analysis.¹⁷

To demonstrate the applicable potency of our transformation, a multi-gram scale preparation experiment was then performed (Scheme 2). When a solution of **1a** (1.00 g) and **2a** (1.09 g) in MeCN was irradiated by 6 W blue LEDs in an open atmosphere for 24 h, the desired condensation product **3a** was obtained in 94% isolated yield (Scheme 2, **a**). Similarly, when the reaction was scaled up to 61 mmol (6.47 g **1a** was used), it proceeded smoothly without a notable change in terms of the isolated yield (Scheme 2, **b**). To our delight, when the visiblelight promoted dithioacetalization reaction was performed at 61 mmol scale without solvents (neat), **3a** was obtained in 87%



Scheme 2 Multi-gram scale reaction.

yield, which was only slightly less efficient than the standard reaction conditions (Scheme 2, c vs. b). For the above multigram preparation experiments, the obtained 2-phenyl-1,3-diathine **3a** could be easily purified by recrystallization from ethanol which made the work up and purification process greener and more environmentally friendly.¹⁸

In order to clarify the reaction mechanism, several control experiments were conducted whose results are shown in Scheme 3. When the common radical trapping reagent, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 3.0 equiv.) was added into the reaction system, no 3a was obtained and a cross coupling product containing TEMPO and 1,3-propanedithiol fragments was isolated, confirmed by HRMS (Scheme 3, a). The above result indicated that a sulphur radical intermediate might be involved in this transformation which was different from Lei's work.¹³ A previous experiment in the absence of light (Table 1, entry 7) indicated that light irradiation was essential. And a further experiment without air (under N_2 , Scheme 3, **b**) suggested that O_2 in air might react as oxidants to generate the sulphur radical in this dithioacetalization reaction. In addition, when the reaction was performed in the presence of Na₂CO₃, none of 3a was detected which indicated that the weak acidity of thiols also played a vital role in the condensation reactions (Scheme 3, c).

According to the related literature,¹⁹ the existence of sulfur free radical in the system can be indirectly proved by the addition of a free-radical spin-trapping agent DMPO (5,5dimethyl-1-pyrroline N-oxide). Subsequently, such EPR experiments were performed to get some insights into the reaction mechanism. To our delight, as shown in Fig. 1a, when DMPO was added to the reaction of 1a and 2a in MeCN under air with blue LED irradiation for 10 min, a similar distinct EPR signal was identified. The parameters observed for the spin adduct were g = 2.0075, $a_N = 13.43$ G and $a_H = 13.72$ G which were very close to the values reported in the literature.^{19d} So this radical signal was an indirect proof of the existence of sulphur radicals in our reaction system. When DMPO was added to the solution of 2a in MeCN under air with blue LED irradiation for 10 min, the same strong signal peak was also observed (Fig. 1b). The above result suggested that the sulphur radical



Scheme 3 Control experiments.

Field (G)

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Fig. 1 (a) EPR spectra of a mixture of **1a** (0.2 mmol), **2a** (0.22 mmol) and DMPO (0.22 mmol) under air in MeCN (0.6 mL) with blue LED irradiation at room temperature for 10 min. (b) EPR spectra of a solution of **2a** (0.2 mmol) and DMPO (0.22 mmol) in MeCN (0.6 mL) under air with blue LED irradiation at room temperature for 10 min.

a)

Field (G)

of **2a** was formed independently by the single electron transfer oxidation in air under optimized conditions.

On the basis of the above results and the related literature,²⁰ a possible mechanism was thus proposed as shown in Scheme 4. Initially, 1,3-propanedithiol (2a) was partially converted to thiol anion Int 1 and H⁺ followed by the single electron oxidation of lnt 1 by O_2 in air with the assistance of blue LED light to form the thiyl radical Int 2. Subsequently, the addition of thiyl radical lnt 2 to the C=O bond of proton-activated aldehyde Int 3 would lead to radical cation Int 4. There are two possible ways to transform **Int 4** into the final product 3. As shown in path a, Int 4 underwent an unusual 1,7-H shift process to generate radical cation Int 5, followed by an intramolecular cyclization to afford sulphur radical cation Int 6. Finally, Int 6 was reduced to 2-R-1,3-dithian 3 by radical anion O₂⁻. In path b, **Int 4** was directly reduced to hemiacetal **Int 7** by radical anion O2^{•-} which was then transformed to 2-R-1,3dithian 3 by the loss of a molecular H₂O and a subsequent cyclization reaction.



Scheme 4 Plausible mechanism.

Conclusions

In conclusion, we have, for the first time developed a simple and convenient visible-light-induced strategy for the dithioacetalization of aldehydes with thiols using air as the environmentally begin oxidant. The developed synthesis protocol proceeds with the merits of mild conditions, broad substrate scope, operation simplicity, high atom efficiency, eco-energy source, green solvent, metal-free photocatalysis and ambient conditions. Further studies into the detailed mechanism of this process as well as the synthesis applications are still ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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- 17 The crystallographic data for compound **7i**, CCDC 1850380.[†]
- 18 Although the neat reaction of **1a** and **2a** gave a satisfied yield with gram scale, this reaction required a homogenies system to make good use of the LED light irradiation. The mixtures of most aldehydes and thiols are heterogeneous at the tested small scale, and the corresponding outcomes are lower than those with acetonitrile as solvents. So the

latter is a more general reaction condition and we choose it as the optimal conditions to screen the scope and limitations of this condensation reaction.

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