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Visible light photoredox catalyzed deprotection of 1,3-oxathiolanes†

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An efficient visible light photoredox catalyzed aerobic deprotection of 1,3-oxathiolanes using organic dye Eosin Y as a photocatalyst is disclosed. The deprotection procedure features the use of a metal-free catalyst, mild conditions, a broad range of substrate scope, and good functional group tolerance. 35 examples were tested under the standard conditions and most of them afforded the deprotected products in modest to high yields.

Introduction

Protecting group manipulation is an essential and important strategy to solve the chemoselectivity problem in modern organic synthesis. A practical protecting group must tolerate the following reaction conditions and be easy to assemble and remove. Among various protecting groups of the ubiquitous carbonyl group in organic molecules, 1,3-oxathiolanes are unique for the following reasons. Firstly, they are more stable than the *O*,*O*-acetal group under acidic conditions and much easier to remove than an *S*,*S*-acetal group; secondly, they can be used as an acyl anion equivalent for carbon–carbon bond forming reactions;[1] finally, chiral 1,3-oxathiolanes can be used for enantioselective synthesis of α-hydroxyaldehydes and related compounds which has been well studied by Eliel and others.[2] Although many methods have been developed for the deprotection of acetals and 1,3-dithiolanes, there are only a few efficient methods for the removal of 1,3-oxathiolanes. Traditionally, 1,3-oxathiolanes can be removed using strong Brønsted acids, Lewis acids and oxidants which are not compatible with many useful and fragile functional groups and seriously limit their applications in modern organic synthesis.[3] Recently, Liu *et al.* reported an efficient LiTMP promoted deprotection of 1,3-oxathiolanes. However, the use of a strong base inevitably subjects the substrates to various side reactions and narrowing functional-group compatibility.[4] Therefore the development of a mild and efficient method to remove this kind of carbonyl protecting group is highly desirable.

Over the past few years, the application of visible light induced photocatalysis has drawn increasing attention in synthetic organic chemistry due to its unique reactivity, mild reaction conditions and the natural abundance of visible light.[5] Importantly, several commercially available organic dyes such as $MesAcr^+$, Eosin Y and 4CzIPN, have been successfully applied to photoredox reactions under metal-free conditions.[6] A detailed literature search revealed that there are two precedential reports regarding photo-catalyzed aerobic deprotection of 1,3-oxathiolanes. The Fasani group firstly reported an elegant photosensitive aerobic deprotection reaction of 2-methyl-2-*tert*-butyl-1,3-dithiolane under irradiation from a high energy phosphor coated lamp using several common photosensitizers as catalysts (Scheme 1b).[7] However, when 2-*tert*-butyl 1,3-oxathiolane (R = H) was tested, the corresponding 2,2-dimethylpropanal was obtained in low yield (≤20%). Lamb and co-workers[8] reported that the 1,3-oxathiolane protecting groups of aryl ketones could be removed by photoirradiation using Rose Bengal as a photocatalyst in the presence of air. Their method was still not effective for the deprotection of 1,3-oxathiolanes prepared from aldehydes (Scheme 1b). Inspired by the above reported results and our research interest in visible light promoted organic transformations,[9] we herein disclose a mild and efficient visible light-induced aerobic deprotection of 1,3-oxathiolanes, providing the corresponding aldehydes or ketones in modest to high yields.

Results and discussion

Initially, 2-(4-bromophenyl)-1,3-oxathiolane **1a** was chosen as a model substrate to screen the optimal deprotection conditions. As shown in Table 1, the desired product **2a** was obtained in 88% yield when the reaction was performed in acetonitrile (MeCN) with Eosin Y as the photocatalyst (Table 1, entry 1). Next, different photocatalysts were examined and it was found

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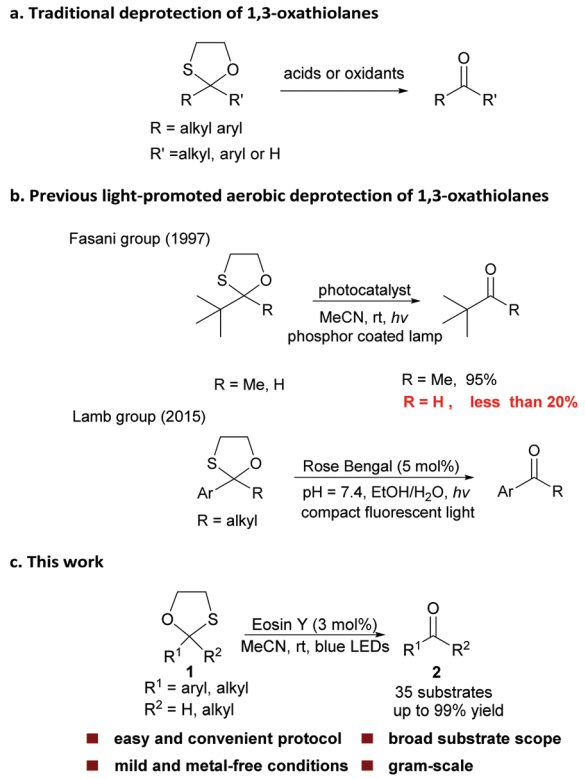
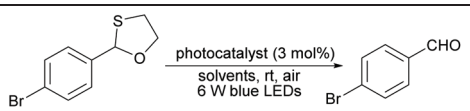


Scheme 1 Methods of deprotection of 1,3-oxathiolanes.

Table 1 Optimization of the deprotection reaction conditions[a]



Entry	Photocatalyst	Solvent	Yield[b] [%]
1	Eosin Y	MeCN	88 (80)[c]
2	Methylene blue	MeCN	71
3	Acid red 87	MeCN	68
4	Rhodamine B	MeCN	24
5	$Ru(bpy)_2Cl_2$	MeCN	70
6	Eosin Y	Toluene	50
7	Eosin Y	THF	78

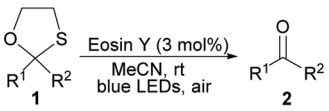
[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.) and the photocatalyst (3 mol%) were added into the solvent (1.5 mL), and the mixture was stirred in air at room temperature for 3 h under irradiation from a 6 W blue LED lamp. [b] Yields determined by ^{1}H NMR spectroscopy using benzyl benzoate as an internal standard. [c] Isolated yield.

that Eosin Y showed the best reactivity (Table 1, entries 1–5). The deprotection reaction could also proceed smoothly in the presence of methylene blue, acid red 87 or $Ru(bpy)_2Cl_2$ as photocatalysts instead, albeit with somewhat lower efficiencies (Table 1, entry 1 *vs.* entries 2, 3 and 5). It was found that Rhodamine B was not an effective photocatalyst (Table 1, entry 4). Different solvents were screened and acetonitrile turned out to be the best choice of solvents compared with toluene and THF (Table 1, entry 1 *vs.* entries 6 and 7). Thus the optimal reaction conditions were as follows: 3 mol% Eosin Y as the photocatalyst and acetonitrile as the solvent (Table 1, entry 1, standard conditions).

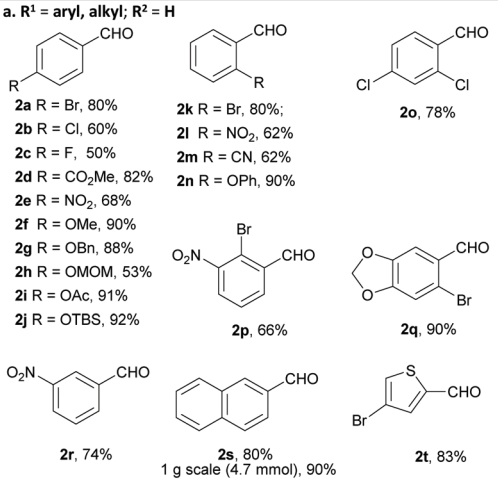
With the optimal conditions in hand, the substrate scope of the deprotection reaction was studied and the results are shown in Table 2. 2-Aryl-1,3-oxathiolanes with electron withdrawing or donating substituents at the *para* position of the phenyl ring were initially screened under the standard conditions (Table 2, **2a–2j**). Generally speaking, the substrates with electron donating groups at the *para* position of the phenyl ring gave slightly higher yields of the corresponding aldehydes (Table 2, **2f–2j**) compared to those with electron withdrawing groups at the same position (Table 2, **2a–2e**). It should be noted here that several common protecting groups for phenols, such as OMOM, OAc and OTBS, were all tolerable under the reaction conditions (Table 2, **2h–2j**) which demonstrated the mildness of our protocol. Additionally, substrates with a substituent at the *ortho* position of the phenyl ring were also explored to determine the steric effects of the deprotection reaction (Table 2, **2k–2n**). There were slight differences in the yields of the obtained aryl aldehydes with the same substituents at the *para*, *ortho* or *meta* position of the phenyl ring (Table 2, **2a** *vs.* **2k**; **2e** *vs.* **2l** *vs.* **2r**) which indicated that the steric hindrance did not affect the deprotection reaction significantly. In fact, even the substrate with a bulky *ortho*-substituted phenoxy group could undergo the deprotection reaction smoothly to give the corresponding aldehyde in 90% yield (Table 2, **2n**). 2-Aryl-1,3-oxathiolanes with multiple substituents on the aryl ring also proved to be suitable substrates in the deprotection reaction (Table 2, **2o–2q**). Both 2-(naphthalen-2-yl)-1,3-oxathiolane and 2-(4-bromothiophen-2-yl)-1,3-oxathiolane underwent the deprotection reaction to give the corresponding aryl aldehydes in 80% and 83% yields, respectively (Table 2, **2s**, **2t**). A gram scale experiment of **1s** under the standard conditions gave aldehyde **2s** in 90% yield which also demonstrated the practical value of our protocol in fine chemical preparation. More significantly, 2-alkyl (or alkenyl)-1,3-oxathiolanes could also participate in the deprotection reaction to give the corresponding aldehydes in modest yields (Table 2, **2u–2y**). It should be noted that the TBDPS (Table 2, **2w**) and Boc (Table 2, **2y**) protecting groups of the substrates remained unaltered during the reaction process which demonstrated the selective deprotection potential of our method. Further testing 2-aryl-2-methyl-1,3-oxathiolanes under the standard conditions gave the corresponding acetophenones in excellent to high yields which also demonstrated the generality of our protocol (Table 2, **2aa–2af**). 1,3-Oxathiolanes derived from aliphatic ketones also proved to be suitable substrates for this deprotection reaction (Table 2, **2ag–2aj**). Notably, large aliphatic cyclic ketone **2ag** and hindered ketone **2ai** could be obtained in high yields under the standard conditions starting from the corresponding 1,3-oxathiolanes.

Several control experiments were conducted to gain a deep insight into the possible mechanism (Scheme 2). As could be seen, the photocatalyst, visible light-irradiation and air were all indispensable for the deprotection reaction to proceed

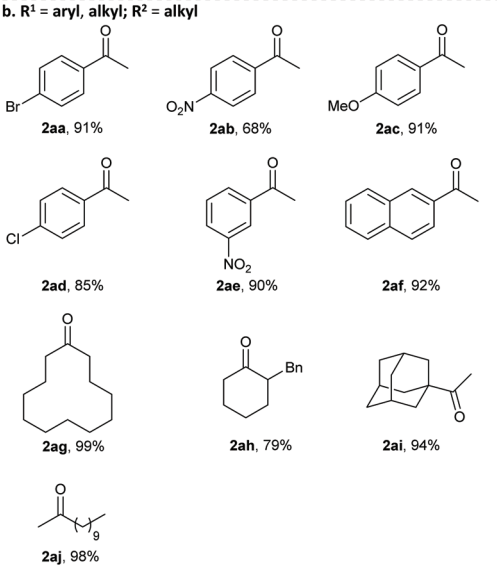
Table 2 Scope of the deprotection reaction[a]



a. R^1 = aryl, alkyl; R^2 = H

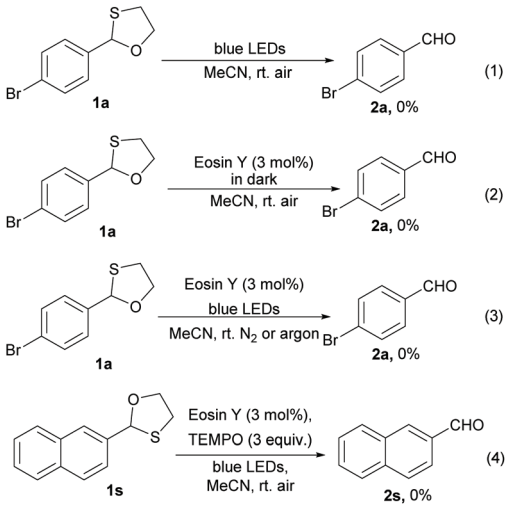


b. R^1 = aryl, alkyl; R^2 = alkyl



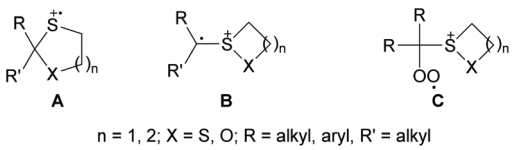
[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv.) and Eosin Y (3 mol%) were added into MeCN (1.5 mL), and the mixture was stirred in air at room temperature for 3 h under irradiation from a 6 W blue LED lamp.

(Scheme 2, eqn (1)–(3)). Addition of TEMPO to the deprotection reaction of **1s** completely inhibited the process (Scheme 2, eqn (4)), thus suggesting the involvement of key radical intermediates along the reaction pathway.



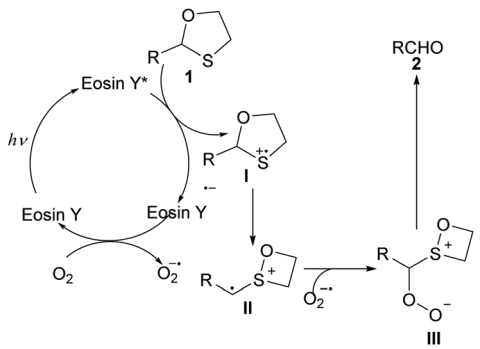
Scheme 2 Control experiments.

a. Key intermediates in previous related mechanism studies



n = 1, 2; X = S, O; R = alkyl, aryl, R' = alkyl

b. Our proposed reaction mechanism



Scheme 3 Proposed mechanism.

Kamata *et al.* proposed that radical cations **A–C** (Scheme 3a, n = 1, 2; X = S) were involved in the reaction process when they studied triphenylpyrylium salt photosensitized catalyzed SET reactions of 1,3-dithianes and 1,3-dithiolanes in the presence of molecular oxygen.[10] Fasani *et al.* also mentioned the involvement of the above three key intermediates (n = 1, X = O, R = ^{t}Bu, R′ = Me) in their discussion about the possible mechanism of photosensitized aerobic deprotection of 1,3-oxathiolanes.[7] Based on the above previous related mechanism studies and the results of control experiments, a possible mechanism of this reaction is shown in Scheme 3. Firstly, Eosin Y is irradiated with blue LED light to generate the active species Eosin Y* in its excited state. Then Eosin Y* was quenched with the oxathiolane to give radical cation **I** and radical anion Eosin

$Y^{\bullet-}$. Eosin $Y^{\bullet-}$ has strong reduction potential and reduces O_2 to super $O_2^{\bullet-}$ and regenerates the photocatalyst Eosin Y. On the other hand, intermediate **I** was subsequently transformed to radical cation **II** which combined with $O_2^{\bullet-}$ to afford peroxide **III**. Finally the fragmentation of peroxide **III** gave the corresponding aldehyde. The final fragmentation step was not very clear at this stage since no useful intermediate was captured using a GC-MS analysis of the reaction mixture.

Experimental

General procedure for the deprotection reaction

1,3-Oxathiolane **1a** (122 mg, 0.5 mmol) and Eosin Y (10 mg, 3 mol%) were added into MeCN (1.5 mL) in a 10 mL clear Pyrex glass tube. The resulting mixture was stirred with a Teflon-coated magnetic stir bar in air at room temperature for 3 h under visible-light irradiation generated from 6 W blue LEDs. After completion of the reaction, the solvent was removed under reduced pressure with a rotary evaporator and the residue was purified by flash column chromatography on silica gel to give the desired 4-bromobenzaldehyde (**2a**) as a white solid (74 mg, 80%).

Conclusions

In summary, an efficient visible-light promoted aerobic deprotection of 1,3-oxathiolanes was developed. Our method featured advantages such as mild conditions, good tolerance of the functional group and easy performance which will expand the application of the 1,3-oxathiolane protecting group in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 E. L. Eliel and S. Morris-Natschke, *J. Am. Chem. Soc.*, 1984, **106**, 2937–2942.
2 (*a*) J. E. Lynch and E. L. Eliel, *J. Am. Chem. Soc.*, 1984, **106**, 2943–2948; (*b*) K. Utimoto, A. Nakamura and S. Matsubara, *J. Am. Chem. Soc.*, 1990, **112**, 8189–8190.
3 (*a*) F. Shirini, P. Sadeghzadeh and M. Abedini, *Chin. Chem. Lett.*, 2009, **20**, 1457–1460; (*b*) S. P. Chavan, P. Soni and S. K. Kamat, *Synlett*, 2001, 1251–1252; (*c*) E. Mondal, P. R. Sahu, G. Bose and A. T. Khan, *Tetrahedron Lett.*, 2002, **43**, 2843–2846; (*d*) T. Ravindranathan, S. P. Chavan, J. P. Varghese, S. W. Dantale and R. B. Tejwani, *J. Chem. Soc., Chem. Commun.*, 1994, 1937–1938; (*e*) T. Ravindranathan, S. P. Chavan and M. M. Awachat, *Tetrahedron Lett.*, 1994, **35**, 8835–8838; (*f*) T. Ravindranathan, S. P. Chavan and S. W. Dantale, *Tetrahedron Lett.*, 1995, **36**, 2285–2288; (*g*) J. S. Yadav, B. V. S. Reddy, S. Raghavendra and M. Satyanarayana, *Tetrahedron Lett.*, 2002, **43**, 4679–4681; (*h*) M. Kirihara, Y. Ochiai, N. Arai, S. Takizawa, T. Momose and H. Nemoto, *Tetrahedron Lett.*, 1999, **40**, 9055–9057; (*i*) S. P. Chavan, S. W. Dantale, K. Pasupathy, R. B. Tejwani, S. K. Kamat and T. Ravindranathan, *Green Chem.*, 2002, **4**, 337–338; (*j*) N. Iranpoor, H. Firouzabadi and H. R. Shaterian, *Tetrahedron Lett.*, 2003, **44**, 4769–4773; (*k*) N. Komatsu, A. Taniguchi, S. Wada and H. Suzuki, *Adv. Synth. Catal.*, 2001, **343**, 473–480.
4 B. Du, C. Yuan, L. Zhang, L. Yang and B. Liu, *Tetrahedron Lett.*, 2013, **54**, 2217–2220.
5 (*a*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113; (*b*) J. Xuan and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828–6838; (*c*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (*d*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166; (*e*) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035–10074; (*f*) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898–6926; (*g*) L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034–10072.
6 D. A. Nicewicz and T. M. Nguyen, *ACS Catal.*, 2014, **4**, 355–360.
7 E. Fasani, M. Freccero, M. Mella and A. Albini, *Tetrahedron*, 1997, **53**, 2219–2232.
8 B. M. Lamb and C. F. Barbas III, *Chem. Commun.*, 2015, **51**, 3196–3199.
9 (*a*) Z. Xing, M. Yang, H. Sun, Z. Wang, P. Chen, L. Liu, X. Wang, X. Xie and X. She, *Green Chem.*, 2018, **20**, 5117–5122; (*b*) S. Feng, X. Xie, W. Zhang, L. Liu, Z. Zhong, D. Xu and X. She, *Org. Lett.*, 2016, **18**, 3846–3849.
10 (*a*) M. Kamata, Y. Kato and E. Hasegawa, *Tetrahedron Lett.*, 1991, **32**, 4349–4352; (*b*) M. Kamata, Y. Murakami, Y. Tamagawa, M. Kato and E. Hasegawa, *Tetrahedron*, 1994, **50**, 12821–12828.