Organic LETTERS

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Visible-Light-Mediated Thiol–Ene Reactions through Organic Photoredox Catalysis

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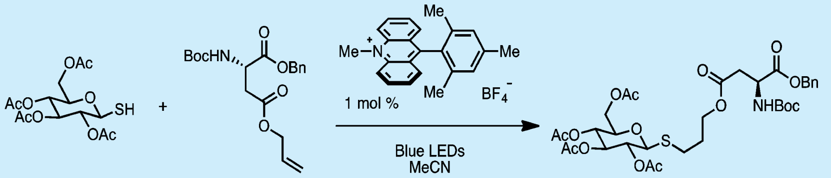
Supporting Information

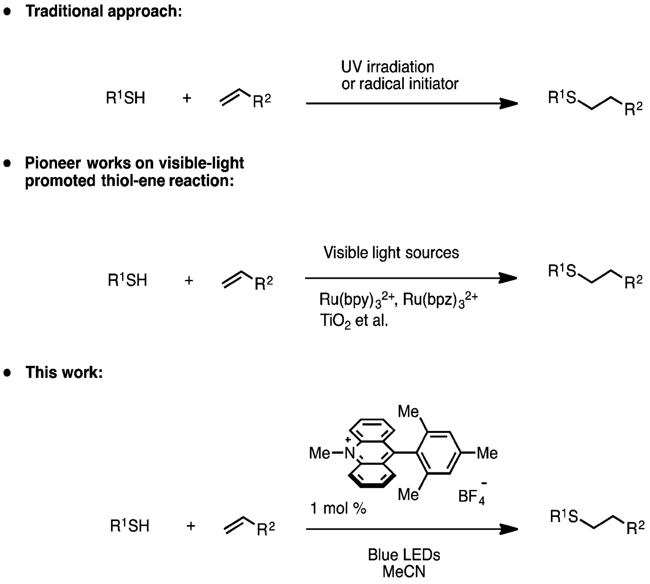


ABSTRACT: Synthetically useful radical thiol–ene reactions can be initiated by visible-light irradiation in the presence of an organic photocatalyst, 9-mesityl-10-methylacridinum tetrafluoroborate. The key thiyl radical intermediates are generated upon quenching of the photoexcited catalyst with a variety of thiols. The success of this method requires only the use of near-stoichiometric levels of alkene coupling partners. Using these highly efficient metal-free conditions, thiol–ene reactions between carbohydrates and peptides can be accomplished in excellent yields.

Carbon–sulfur bond-forming reactions are synthetically important because organosulfur moieties are widely represented within natural products, pharmaceuticals, and modern materials.[1,2] Among various carbon–sulfur bond formations, the thiol–ene reaction, a radical addition of thiols to olefins, is arguably one of the most powerful current methods because of its widespread employment in areas of bioconjugate chemistry, polymer science, and pharmaceutical chemistry.[3,4] This atom-economical process provides efficient and selective access to anti-Markovnikov thioethers, fulfilling the "click" chemistry concept.[5] Traditionally, the radical thiol–ene reaction is promoted by UV light or a radical initiator (Scheme 1).[4d] However, it either needs stoichiometric reagents or requires expensive specialized UV photochemical equipment. Recently, Yoon[6] and Stephenson[7] reported the transition-metal-mediated photoredox catalysis of thiol–ene reactions driven by household visible-light sources as a convenient alternative to UV irradiation (Scheme 1). In addition, other catalyst types, such as TiO_2,[8] have shown the ability to promote thiol–ene reactions when combined with visible-light irradiation.[9] The visible-light photoredox catalysis approach to thiol–ene chemistry provides a significantly milder reaction medium that could be potentially useful in bioconjugation and polymer synthesis.[10]

In the works by Yoon and Stephenson, both Ru(bpy)$_3^{2+}$ ($E_{1/2}^{\mathrm{red}}$[*Ru$^{\mathrm{II}}$/Ru$^{\mathrm{I}}$] = +0.77 V vs SCE) and Ru(bpz)$_3^{2+}$ ($E_{1/2}^{\mathrm{red}}$[*Ru$^{\mathrm{II}}$/Ru$^{\mathrm{I}}$] = +1.35 V vs SCE) were extensively studied.[11] Interested in seeking a metal-free opportunity,[12] we report herein that a more powerful oxidizing organic catalyst, 9-mesityl-10-methylacridinum tetrafluoroborate ($E_{1/2}^{\mathrm{red}}$ = +2.06 V vs SCE in MeCN), can serve as an effective visible-light photoinitiator of the thiol–ene reaction (Scheme 1).[13,14] This photoredox process driven by an organic photocatalyst is synthetically complementary to both traditional (using UV irradiation or thermolysis of a radical initiator) and transition-metal-mediated approaches. In particular, a metal-free process could potentially benefit peptide and glycoprotein chemistry, since certain polypeptide sequences and proteins have been shown to interfere with transition-metal-mediated processes.[15]

Scheme 1. Radical Thiol–Ene Reactions



To test the idea, we started our investigations by examining the thiol–ene reaction between benzyl mercaptan (**1**) ($E_{1/2}^{\mathrm{red}}$ = +0.45 V vs SCE)[16] and allyl alcohol (**2**) (Table 1). After a survey of

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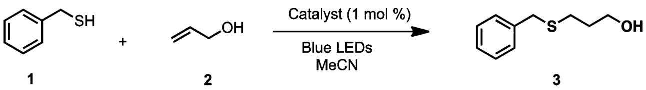
Table 1. Optimization Studies for the Thiol–Ene Reaction of Benzyl Mercaptan with Allyl Alcohol[a]

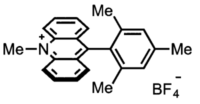


1 2 3

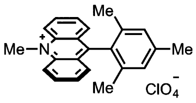
1 equiv 1.2 equiv

entry	catalyst	yield[b] (%)
1	**A**	90
2	**B**	83
3	**C**	69
4	rhodamine 6G	80
5	riboflavin	0
6	eosin Y	30
7	rose bengal	33
8	methylene blue	0
9	none	0
10[c]	**A**	0

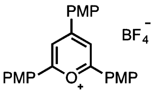
[a]Reactions were conducted by irradiating **1** (0.5 mmol), **2** (0.6 mmol), and the photocatalyst (1 mol %) in MeCN (1 mL) with two 12 W, 450 nm LED floodlamps for 6 h. [b]Isolated yields. [c]The reaction was conducted in the dark.



A

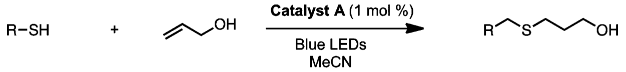


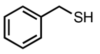
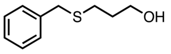
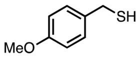
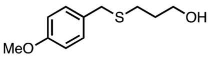
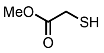
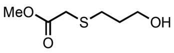
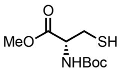
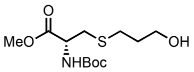
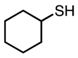
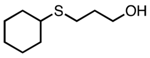
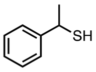
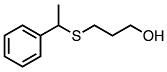
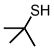
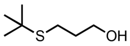
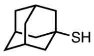
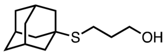
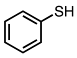
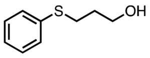
B



C

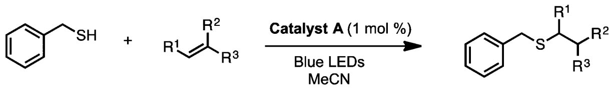
Table 2. Scope of Thiols[a]

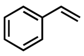
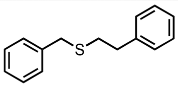
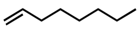
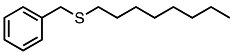
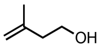
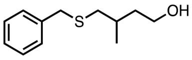
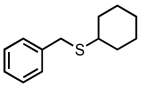
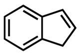
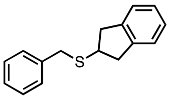
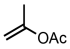
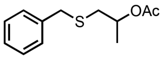
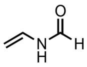
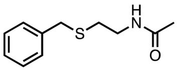
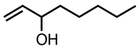
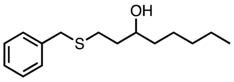
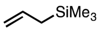
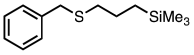


entry	thiol	product	yield[b] (%)
1			90
2			87
3			82
4			86
5			90
6			83
7			85
8			77
9			88

[a]Reactions were conducted by irradiating the thiol (0.5 mmol), allyl alcohol (0.6 mmol), and photocatalyst **A** (1 mol %) in MeCN (1 mL) with two 12 W, 450 nm LED floodlamps for 6 h. [b]Isolated yields.

Table 3. Scope of Alkenes[a]



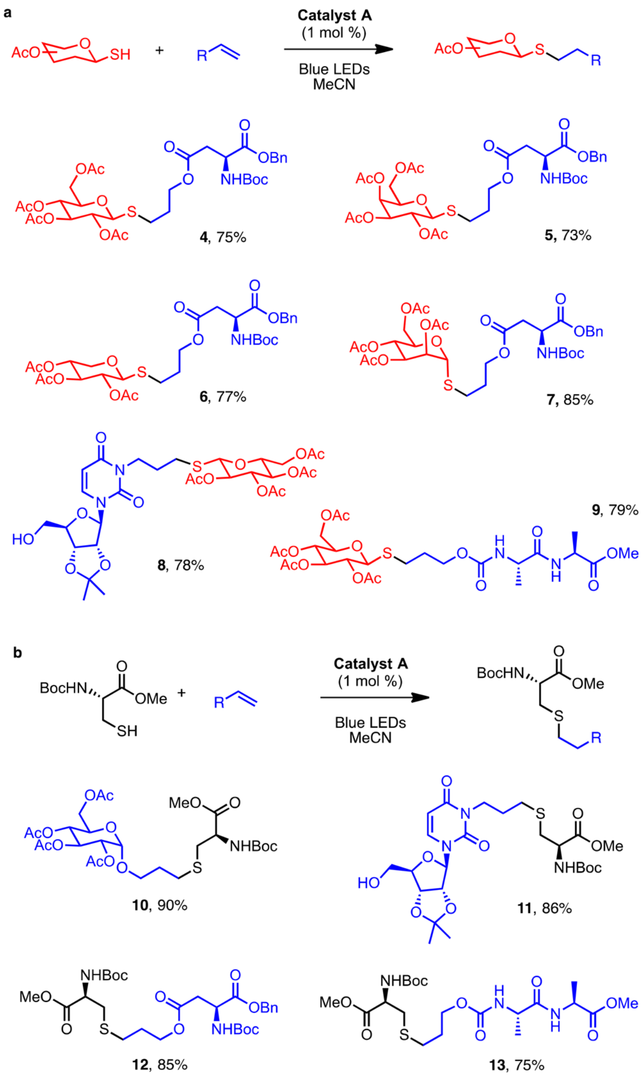
entry	alkene	product	yield[b] (%)
1			76
2			87
3			83
4			83
5			80
6			86
7			82
8			85
9			80

[a]Reactions were conducted by irradiating benzyl mercaptan (0.5 mmol), the alkene (0.6 mmol), and photocatalyst **A** (1 mol %) in MeCN (1 mL) with two 12 W, 450 nm LED floodlamps for 6 h. [b]Isolated yields.

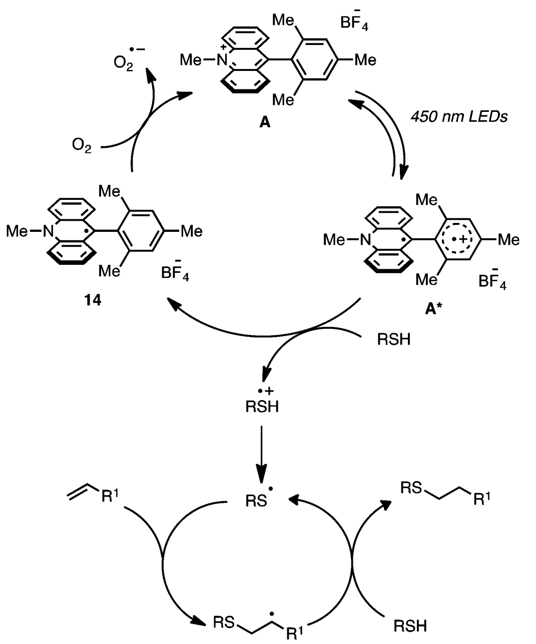
organic photocatalysts (entries 1−8), we were pleased to observe that 9-mesityl-10-methylacridinum tetrafluoroborate (**A**) successfully initiated the photocatalytic thiol−ene reaction under blue light-emitting diode (LED) irradiation, providing the thiol−ene adduct **3** in 90% isolated yield. It is worth noting that only a minimal excess of alkene (1.2 equiv) is required for full conversion of thiol to product. In addition, MeCN was found to be the optimal solvent after careful screening of various solvents (CH_2Cl_2, DMF, DMSO, THF, 1,4-dioxane, MeOH, and toluene). Control experiments (entries 9 and 10) verified that both the catalyst and the LED irradiation are necessary.

Encouraged by these results, we next focused our attention on exploring the scope of the photocatalytic thiol−ene reaction. Table 2 summarizes experiments probing a variety of thiols that can be activated using the optimized conditions. Primary thiols such as benzyl mercaptan (entry 1), *p*-methoxybenzyl mercaptan (entry 2), methyl thioglycolate (entry 3), and a protected cysteine derivative (entry 4) reacted with allyl alcohol efficiently to generate hydrothiolated products in high yields. Secondary thiols such as cyclohexyl mercaptan (entry 5) and 1-phenylethyl mercaptan (entry 6) also produced thiol−ene adducts successfully. Happily, even sterically encumbered *tert*-butyl mercaptan (entry 7) and 1-adamantylthiol (entry 8) afforded good yields. In addition, aromatic thiols such as thiophenol (entry 9) were converted into the corresponding aryl thioethers in high yield under these conditions.

Scheme 2. Visible-Light-Mediated Thiol−Ene Conjugations



Scheme 3. Proposed Mechanism



Next, we evaluated the scope of alkenes that can participate in this coupling process (Table 3). Both styrene and aliphatic alkenes reacted smoothly under these reaction conditions (entries 1 and 2). We were pleased to find that both 1,1-disubstituted (entry 3) and 1,2-disubstituted (entries 4 and 5) alkene substrates underwent successful thiol−ene reaction with benzyl mercaptan. In all cases, high anti-Markovnikov regioselectivity was observed, which is consistent with the proposed radical reaction process. Moreover, this radical thiol−ene process is compatible with a variety of functional groups, as ester (entry 6), formyl amide (entry 7), alcohol (entry 8), and silane (entry 9) are tolerated under these conditions.

Having demonstrated the high efficiency of the visible-light-mediated thiol−ene reaction, we next investigated the applicability of this chemistry to enable the synthesis of glycoconjugates between glycosyl thiols and amino acid derivatives (Scheme 2). Glycoconjugates have become important tools for the exploration of many biological processes,[17,18] and more recently, S-linked glycoconjugates have become promising analogues of glycopeptides and glycoproteins because of their enhanced chemical stability and enzymatic resistance.[19,20] Happily, the thiol−ene reaction between an aspartic acid derivative and a variety of glycosyl thiols occurred smoothly (Scheme 2a), giving the corresponding S-linked glycoconjugates **4**−**7** in good yields. More complex examples serve to demonstrate the potential utility of this method for bioconjugation. We observed efficient coupling of glucose thiol with a nucleoside derivative and an N-terminus-functionalized dipeptide, affording S-linked glyconucleoside **8** and glycopeptide **9** in yields of 78% and 79%, respectively. The reverse fashion of coupling between a protected cysteine derivative and a variety of alkenes also provided excellent yields of the conjugated products **10**−**13** (Scheme 2b).

A reasonable mechanism for the reaction is outlined in Scheme 3. Photoexcitation of catalyst **A** provides a strongly oxidizing state (**A***) that can oxidize a thiol to generate the thiyl radical cation and one-electron-reduced acridinium **14**. The proposed preference for oxidation of the thiol over the alkene relies on the difference in their reduction potentials.[14o,16] Deprotonation of the radical cation generates a thiyl radical, which couples to the alkene with anti-Markovnikov selectivity. The resulting alkyl radical then abstracts a hydrogen atom from an unreacted thiol to afford the thiol−ene product and generate another equivalent of thiyl radical. However, the light irradiation is necessary for the reaction to reach completion on the basis of our experimental results (Scheme S1 in the Supporting Information). It is likely that the catalyst is reoxidized by a molecule of oxygen, regenerating the photoactive catalyst **A**.

In summary, we have reported a visible-light-promoted radical thiol−ene reaction using catalytic amounts of 9-mesityl-10-methylacridinum tetrafluoroborate. This highly efficient reaction shows scope generality, as demonstrated by the use of a variety of thiols and alkenes to provide thioethers in excellent yields. Moreover, this method demonstrates promise for future glycoprotein studies through the successful generation of model glycoconjugates. Applications of this thiol−ene reaction in more complicated bioconjugate settings are ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01441.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(3) For the utility of thiyl radicals in organic synthesis, see: Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587.

(4) For applications of the thiol−ene reaction, see: (a) Hoyle, C. E.; Lee, T. Y.; Roper, T. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 5301. (b) ten Brummelhuis, N.; Diehl, C.; Schlaad, H. *Macromolecules* **2008**, *41*, 9946. (c) Sletten, E.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974. (d) Hoyle, C. E.; Bowman, C. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540.

(5) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231.

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