Tetrahedron Letters 86 (2021) 153499

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Radical functionalization of thioglycosides in aqueous medium

Sarbjeet Kaur, Dominic P. Luciano [1], Xinhao Fan, Gaoyuan Zhao [2], Sheridan Messier, Madison M. Walker, Qiang Zhang, Ting Wang *

Department of Chemistry, University at Albany, State University of New York, 1400 Washington Avenue, Albany, NY 12222, United States

ARTICLE INFO

Article history:
Received 9 September 2021
Revised 17 October 2021
Accepted 18 October 2021
Available online 22 October 2021

ABSTRACT

A visible-light-mediated thiol-ene reaction is successfully operated in aqueous medium. An organic photoredox catalyst (9-mesityl-10-methylacridinum tetrafluoroborate) is used to initiate the radical process to generate thiyl radicals upon light irradiation. Two reaction pathways were discovered in different aqueous buffer systems. A thiol-ene adduct is preferred in acidic reaction medium; while disulfide formation is found to be favored in basic reaction medium. The photocatalytic method is demonstrated to be applicable on unprotected peptides.

Sulfur radicals have played important roles in many biological systems. For example, the cysteine residue in many proteins, such as thioredoxin, could serve as the sulfur radical precursor [1–2]. The resulting sulfur radicals are heavily involved in a variety of enzymatic processes [1]. Inspired by nature, these sulfur radicals have also attracted significant attention in the synthetic community [3–4]. Traditionally, the use of radical initiators or UV irradiation on thiols or disulfides has led to the formation of sulfur radicals. These can react with a multitude of radical acceptors, such as alkenes in a thiol-ene reaction, and alkynes in a thiol-yne reaction [5]. Particularly, the thiol-ene reaction is a powerful method that has been widely employed in areas of bioconjugate chemistry, polymer science, and pharmaceutical chemistry [3–4]. Recently, visible-light photoredox catalysis has been developed into a useful tool in organic synthesis [6]. The use of this strategy in a thiol-ene reaction [7] excluded the need of a stoichiometric radical initiator or expensive specialized UV photochemical equipment. In 2013, Yoon reported the first visible-light photoredox catalyzed thiol-ene reaction using $Ru(bpz)_3^{2+}$ as a photocatalyst [8]. In the following years, several groups, including our group, have reported visible-light-mediated thiol-ene reactions through the use of various photocatalysts [9–10]. This visible light photocatalytic thiol-ene strategy provided a much milder reaction condition, which has the potential to be useful in a variety of synthetic applications.

While sulfur radical reactions have previously been conducted in organic solvents, it has been shown that they may also be able to be performed in aqueous medium. This is due to the fact that the alky RS-H bond (BDE = ~87 kcal/mol) is weaker than the HO-H bond (BDE = ~119.3 kcal/mol), meaning that sulfur radicals will not be quenched in H_2O. This indicates that aqueous medium is a promising solvent to conduct sulfur radical reactions in. This has the potential to expand the scope of sulfur radical reactions in glycopeptides' synthesis due to the poor solubility of protected peptides in organic solvents and the difficulty of purification of protected peptides. In 1998, Oshima and co-workers reported a radical addition of benzenethiol (**1**) to *N*-acetyldiallylamine (**2**) in water, affording *N*-acetylpyrrolidine derivative **3** (Scheme 1a) [11]. In addition to this application in small molecule synthesis, the Danishefsky-Wan desulfurization significantly broadens the synthetic merits of the native chemical ligation (NCL) in peptide and protein synthesis (Scheme 1b) [12]. By using a water-soluble radical initiator (VA-044), the cysteine in a polypeptide (**4**) could be converted to the corresponding alanine (**5**) following a radical mechanism. With such development, the NCL strategy would no longer be limited to the cysteine site. The metal-free process also makes it practically useful in polypeptides and glycopeptides' synthesis. More recently, Davis and co-workers reported a radical thiol-ene reaction which was applied in a convergent synthesis of S-linked glycoconjugates (Scheme 1c) [13].

S-linked glycoconjugates have become useful analogs of glycopeptides and glycoproteins because of their improved chemical stability and enzymatic resistance [14]. Inspired by Davis' thiyl glycosylation work [13], we were also interested in applying our metal-free visible-light-mediated thiol-ene reaction in aqueous medium. Our study was commenced by testing the reaction between glycosyl thiol (**9**) and allyl alcohol (**10**) in water with the presence of a photocatalyst (9-mesityl-10-methylacridinum tetrafluoroborate). Happily, a thiol-ene adduct (**11**) could be obtained in good yield under blue light-emitting diode (LED)

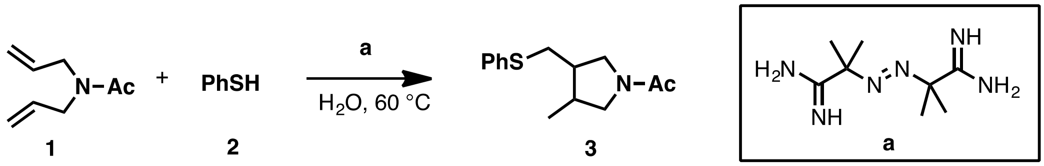
---

* Corresponding author.
E-mail address: twang3@albany.edu (T. Wang).

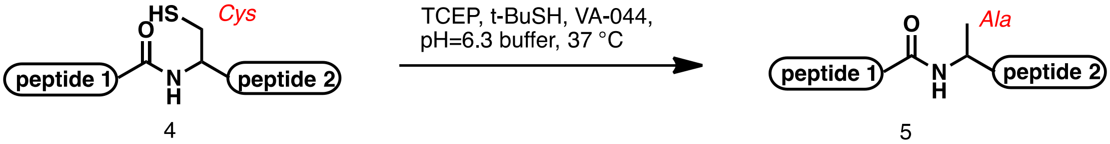
[1] Current address: Biogen, 115 Broadway, Cambridge, MA 02142, United States.

[2] Current address: Department of Chemistry, Stony Brook University, Stony Brook, NY 11794, United States.

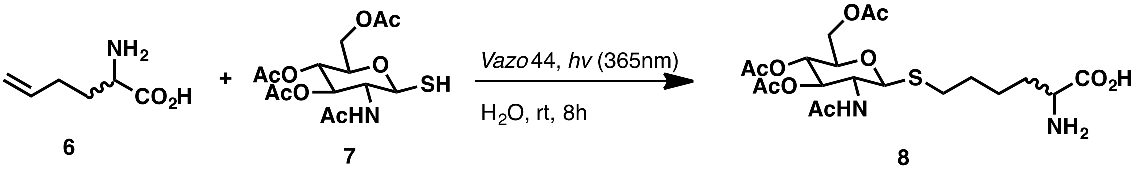
https://doi.org/10.1016/j.tetlet.2021.153499
0040-4039/



b. Danishefsky-Wan desulfurization



c. S-Linked Glycoconjugate synthesis



Scheme 1. Examples of sulfur radical reaction in aqueous medium.

irradiation (72%, Scheme 2a). The reaction performed even better in CH_3CN/H_2O (1:1) mixture, most likely due to the better solubility of the protected glycosyl thiols in this solvent (85%, Scheme 2b). Since the majority of glycoconjugate reactions were performed in aqueous buffers, we next attempted the radical thiol-ene reaction in buffers with common pH values, pH = 6 and pH = 8, respectively (Scheme 2c, 2d). Surprisingly, besides the desired thiol-ene adduct **11**, an unexpected disulfide byproduct **12** was isolated, 12% and 20%, respectively (Scheme 2c, 2d). This indicates that the byproduct formation was enhanced in more basic aqueous medium.

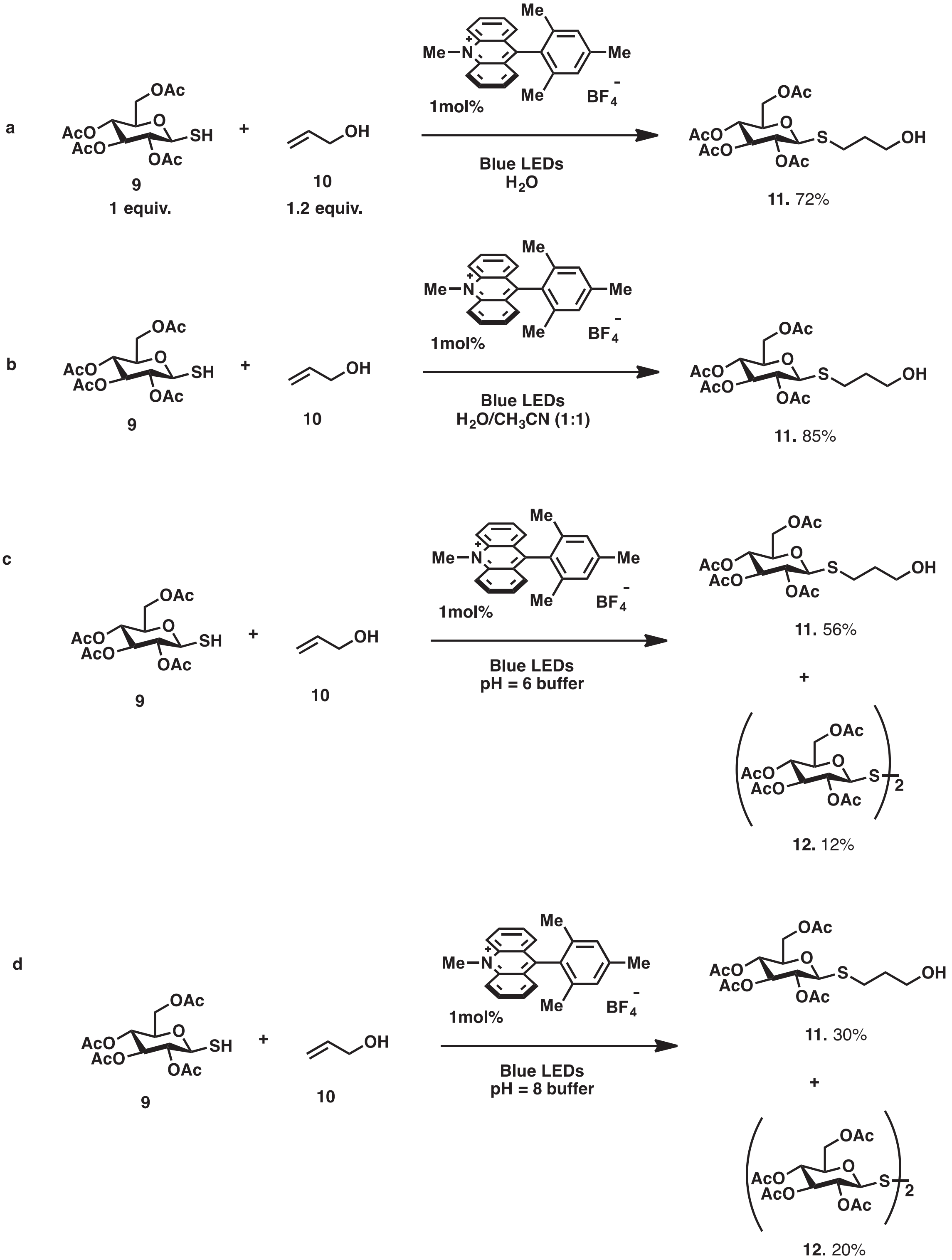
Intrigued by these results, we went back to the organic solvent to check if a base additive would affect the thiol-ene reaction outcome. We have previously reported that the thiol-ene adduct **14** could be afforded in excellent yield between benzyl mercaptan (**13**, 1 equiv.) and allyl alcohol (**10**, 1.2 equiv.) (Scheme 3a) [10]. We then added triethylamine as an additive in a separate reaction (Scheme 3b). Surprisingly, only disulfide product **15** was obtained under such condition with a yield of 70%. This base mediated photocatalytic disulfide formation is consistent with that previously report by Noel. [15] However, the competing reaction pathway between the thiol-ene reaction and the disulfide formation have drawn our interest.

We next carefully screened the effect of the pH value of the aqueous medium on disulfide formation. Davis has reported that some of the glycoconjugate formation favored more acidic medium (pH = 4 in some cases). [13] We then attempted the photocatalytic thiol-ene reaction in a buffer with pH 4 (Table 1, entry 3). Gladly, we observed the suppression of the disulfide formation (5% of **12**, Table 1, entry 3). In contrast, more disulfide byproduct was isolated in more basic medium (pH = 8 buffer, 36% of **12**, Table 1, entry 4). This trend clearly suggested that increasing the acidity of the aqueous medium would favor the thiol-ene reaction, while dimerization would be preferred in more basic medium. Finally, we figured out the dimerization could be completely suppressed in pH = 2.6 buffer, providing thiol-ene product **11** as the only product in 72% (Table 1, entry 5). The control reaction, performed in the dark, (Table 1, entry 6) has shown the light is necessary in this reaction, excluding the possibility of acid-promoted reaction in such acidity medium.

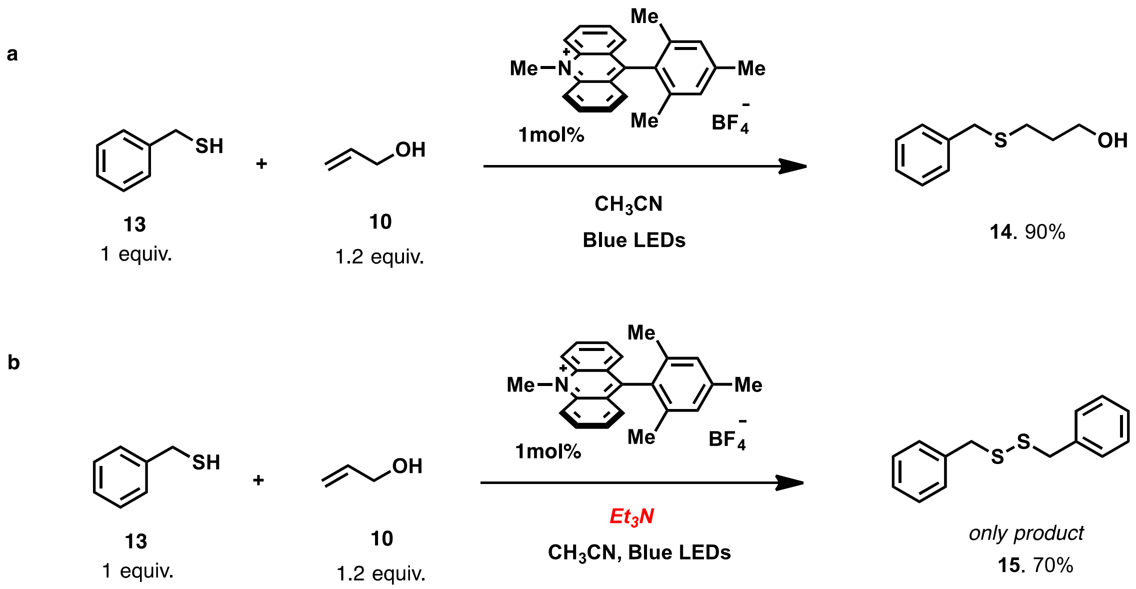
A proposed mechanism for the formation of the thiol-ene product and disulfide byproduct is outlined in Scheme 4. Upon photocatalytic single electron oxidation of thiol (**16**), the key intermediate thiyl radical cation (**17**) would be formed along with one electron reduced acridinium **18** [16–17]. We proposed two pathway in this stage: 1) in acidic medium, a thiyl radical would be released slowly, giving relative low concentration of thiyl radical. A thiol-ene reaction was favored in this pathway, coupling with the alkene with anti-Markovnikov selectivity; 2) on the other hand, a thiyl radical would go through a fast release in basic medium. The relative high concentration of thiyl radical favors the dimerization, affording disulfide product. Oxidation of **18** by a molecule of oxygen would regenerate photocatalyst **A** (Scheme 4).

Encouraged by the success of visible-light mediated radical addition of thioglycosides to alkene in aqueous medium, we next wonder if we could extend the substrate to other thioglycosides and peptide-derived coupling partners, and ultimately apply such photocatalytic method on unprotected peptides. Outlined in Scheme 5, the galactosyl thiol (**18**) reacted with allyl alcohol smoothly in presence of water to afford the thiol-ene adduct **19** in great yield (83%, Scheme 5a). Moreover, the glucosyl thiol could also be efficiently coupled with *N*-terminus functionalized dipeptide (**20**), furnishing S-linked glycopeptide **21** (Scheme 5b) [10]. Finally, an unprotected pentapeptide (**22**) tethering an alkene on the aspartic acid side chain was prepared and subjected to reaction with thioglycoside (**9**) and a photocatalyst in H_2O/CH_3CN. Happily, upon light irradiation, the desired glycopeptide (**19**) was furnished smoothly in 50% isolated yield (Scheme 5c).

Ultimately, we have developed a visible-light-mediated radical functionalization of thioglycoside in aqueous medium. Different reaction pathways were favored in different buffer systems resulting in either a thiol-ene reaction or disulfide formation to predominate. An acidic reaction medium was favored by the thiol-ene reaction. The addition of a base additive resulted in disulfide formation which was increasingly favorable in basic medium.

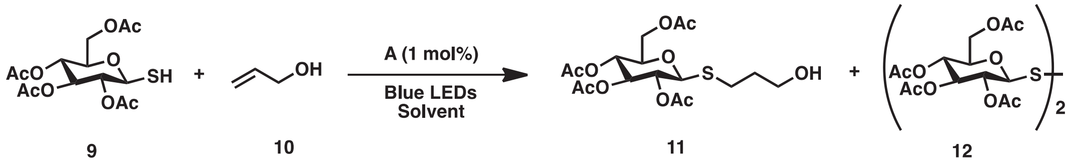


Scheme 2. Visible-light-mediated thiol-ene reaction in aqueous medium.

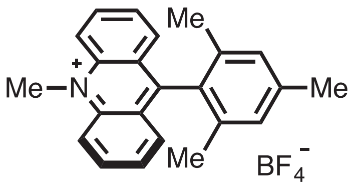


Scheme 3. Base promoted disulfide formation.

Table 1
Visible-light-mediate thiol-ene reaction in buffers.

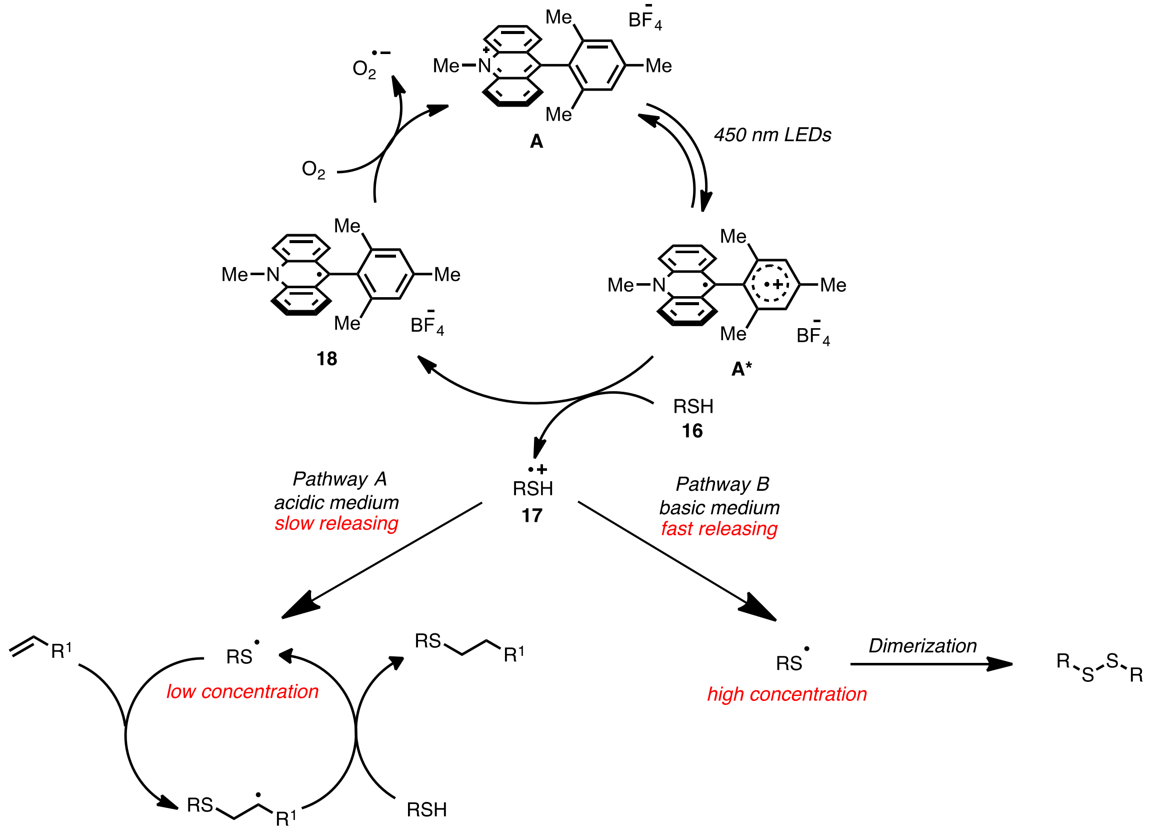


Entry	Catalyst	Solvent	Yield (%)[b] a	Yield (%)[b] b
1	A	Buffer pH = 6	56	12
2	A	Buffer pH = 8	30	20
3	A	Buffer pH = 4	57	5
4	A	Buffer pH = 10	20	30
5	A	Buffer pH = 2.6	72	0
6[c]	A	Buffer pH = 2.6	0	0

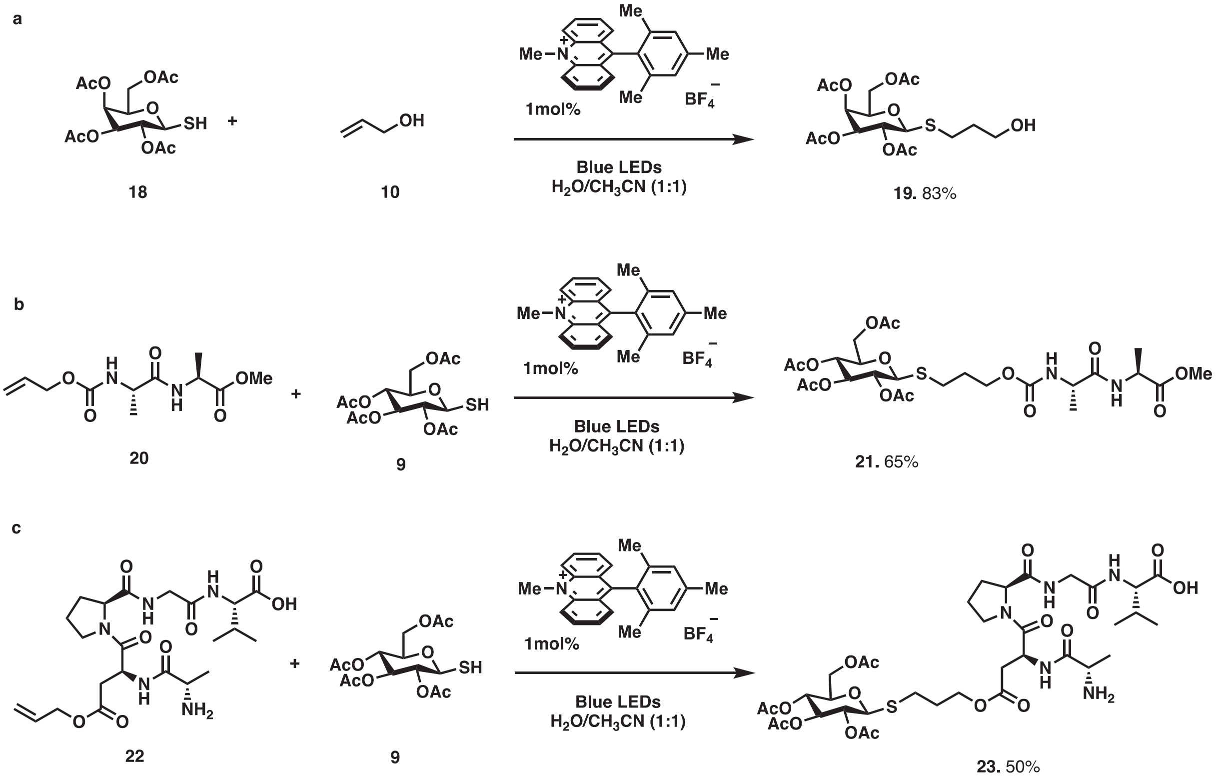


A

[a] Reactions were conducted by irradiating **1** (0.137 mmol), **2** (0.165 mmol), and the photocatalyst (1 mol%) in solvent (0.274 mL) with two 12 W, 450 nm LED floodlamps for 6 h. [b] Isolated yield [c] Reaction was conducted in dark.



Scheme 4. Proposed mechanism.



Scheme 5. Photocatalytic glycoconjugate reaction with unprotected peptide.

Excitingly, the photocatalytic method was also demonstrated to be applicable on unprotected peptides. The application of the photocatalytic thiol-ene reaction between more sophisticated thioglycosides and peptides are ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We are grateful to the University at Albany, State University of New York, for financial support. Support from National Science Foundation (MRI 1726724) and (CHE 1710174) were acknowledged.

References

[1] M. Kolberg, K.R. Strand, P. Graff, K.K. Andersson, Biochim. Biophys. Acta 1699 (2004) 1.

[2] E. Torrents, P. Aloy, I. Gibert, F. Rodríguez-Trelles, J. Mol. Evol. 55 (2002) 138.

[3] P. Chauhan, S. Mahajan, D. Enders, Chem. Rev. 114 (2014) 8807.

[4] F. Dénès, M. Pichowicz, G. Povie, P. Renaud, Chem. Rev. 114 (2014) 2587.

[5] For selective reviews on the applications of the thiol-ene/thiol-yne reaction, see: (a) C. E. Hoyle, T. Y. Lee, T. Roper, *J. Polym. Sci. Part A: Polym. Chem.*, 2004, **42**, 5301; (b) E. Sletten, C. R. Bertozzi, *Angew. Chem. Int. Ed.*, 2009, **48**, 6974; (c) C. E. Hoyle, C. N. Bowman, *Angew. Chem., Int. Ed.*, 2010, **49**, 1540; (d) A. Dondoni, A. Marra, *Chem. Soc. Rev*., 2012, **41**, 573; (e) R. Hoogenboom, *Angew. Chem., Int. Ed.*, 2010, **49**, 3415; (f) A. Massi, D. Nanni, *Org. Biomol. Chem.*, 2012, **10**, 3791; (g) A. B. Lowe, C. E. Hoyle, C. N. Bowman, *J. Mater. Chem.*, 2010, **20**, 4745; (h) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev*., 2011, **111**, 1596; (i) R. Castarlenas, A. Di Giuseppe, J. J. Perez-Torrente, L. A. Oro, *Angew. Chem., Int. Ed.*, 2013, **52**, 211; (j) A. B. Lowe, *Polymer*, 2014, **55**, 5517.

[6] (a) For selected reviews, see: C.K. Prier, D.A. Rankic, D.W.C. MacMillan Chem. Rev. 113 (2013) 5322;
(b) M.N. Hopkinson, B. Sahoo, J.L. Li, F. Glorius, Chem. - Eur. J. 20 (2014) 3874;
(c) M.D. Kärkäs, J.A. Porco Jr., C.R.J. Stephenson, Chem. Rev. 116 (2016) 9683;
(d) J. Xuan, W.-J. Xiao, Angew. Chem., Int. Ed. 51 (2012) 6828;
(e) T.P. Yoon, ACS Catal. 3 (2013) 895;
(f) D.A. Nicewicz, T.M. Nguyen, ACS Catal. 4 (2014) 355;
(g) S. Fukuzumi, K. Ohkubo, Org. Biomol. Chem. 12 (2014) 6059;
(h) D.P. Hari, B. König, Chem. Commun. 50 (2014) 6688;
(i) N.A. Romero, D.A. Nicewicz, Chem. Rev. 116 (2016) 10075;
(j) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, Chem. Soc. Rev. 45 (2016) 2044;
(k) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, Acc. Chem. Res. 2016 (1911) 49;
(l) J.-R. Chen, X.-Y. Yu, W.-J. Xiao, Synthesis (2015) 604;
(m) Y. Liu, R. Song, J. Li, Sci. China: Chem. 59 (2016) 161.

[7] A. Wimmer, B. König, Beilstein J. Org. Chem. 14 (2018) 54.

[8] E.L. Tyson, M.S. Ament, T.P. Yoon, J. Org. Chem. 78 (2013) 2046.

[9] (a) E.L. Tyson, Z.L. Niemeyer, T.P. Yoon, J. Org. Chem. 79 (2014) 1427;
(b) V.T. Bhat, P.A. Duspara, S. Seo, N.S.B. Abu Bakar, M.F. Greaney, Chem. Commun. 51 (2015) 4383;
(c) C.A. DeForest, K.S. Anseth, Nat. Chem. 3 (2011) 925;
(d) C.A. DeForest, K.S. Anseth, Angew. Chem., Int. Ed. 2012 (1816) 51;
(e) H. Shih, C.C. Lin, Macromol. Rapid Commun. 34 (2013) 269;
(f) H. Shih, A.K. Fraser, C.C. Lin, ACS Appl. Mater. Interfaces 5 (2013) 1673;
(g) D. Limnios, C.G. Kokotos, Adv. Synth. Catal. 359 (2017) 323;
(h) O.O. Fadeyi, J.J. Mousseau, Y. Feng, C. Allais, P. Nuhant, M.Z. Chen, B. Pierce, R. Robinson, Org. Lett. 17 (2015) 5756–5759;
(i) M. Singh, A.K. Yadav, L.D.S. Yadav, R.K.P. Singh, Tetrahedron Lett. 58 (2017) 2206–2208;
(j) M.H. Keylor, J.E. Park, C.-J. Wallentin, C.R.J. Stephenson, Tetrahedron 70 (2014) 4264;
(k) H. Choi, M. Kim, J. Jang, S. Hong, Angew. Chem. Int. Ed. 59 (2020) 22514;
(l) V.V. Levin, A.D. Dilman, J. Org. Chem. 84 (2019) 8337.

[10] (a) G. Zhao, S. Kaur, T. Wang, Org. Lett. 19 (2017) 3291;
(b) S. Kaur, G. Zhao, E. Busch, T. Wang, Org. Biomol. Chem. 2019 (1955) 17.

[11] H. Yorimitsu, K. Wakabayashi, H. Shinokubo, K. Oshima, Tetrahedron Lett. 40 (1999) 519.

[12] Q. Wan, S.J. Danishefsky, Angew. Chem. Int. Ed. 46 (2007) 9249.

[13] N. Floyd, B. Vijayakrishnan, J.R. Koeppe, B.G. Davis, Angew. Chem. Int. Ed. 48 (2009) 7798.

[14] (a) D. Horton, J.D. Wander, Carbohydrates: Chemistry and Biochemistry Vol. 4B (1990) 799;
(b) R.T. Dere, X. Zhu, Org. Lett. 10 (2008) 4641;
(c) G.J.L. Bernards, E.J. Grayson, S. Thompson, J.M. Chalker, J.C. Errey, F. El Oualid, T.D.W. Claridge, B.G. Davis, Angew. Chem., Int. Ed. 47 (2008) 2244;
(d) G.J.L. Bernardes, D.P. Gamblin, B.G. Davis, Angew. Chem., Int. Ed. 45 (2006) 4007;
(e) D.P. Gamblin, P. Garnier, S. van Kasteren, N.J. Oldham, A.J. Fairbanks, B.G. Davis, Angew. Chem., Int. Ed. 43 (2004) 827;
(f) S.B. Cohen, R.L. Halcomb, J. Am. Chem. Soc. 124 (2002) 2534;
(g) D.A. Thayer, H.N. Yu, M.C. Galan, C.H. Wong, Angew. Chem., Int. Ed. 44 (2005) 4596;
(h) Y. Zhu, W.A. van der Donk, Org. Lett. 3 (2001) 1189;
(i) Y. Zhu, M.D. Gieselman, H. Zhou, O. Averin, W.A. van der Donk, Org. Biomol. Chem. 1 (2003) 3304;
(j) X. Zhu, K. Pachamuthu, R.R. Schmidt, J. Org. Chem. 68 (2003) 5641;
(k) X. Zhu, R.R. Schmidt, Chem. Eur. J. 10 (2004) 875;
(l) M. Fiore, A. Marra, A.J. Dondoni, Org. Chem. 74 (2009) 4422;
(m) J.R. Rich, A. Szpacenko, M.M. Palcic, D.R. Bundle, Angew. Chem., Int. Ed. 43 (2004) 613;
(n) H. Driguez, Top. Curr. Chem. 187 (1997) 85;
(o) L. Szilagyi, O. Varela, Curr. Org. Chem. 10 (2006) 1745;
(p) H. Driguez, ChemBioChem 2 (2001) 311;
(q) D. Crich, T.J. Ritchie, Carbohydr. Res. 190 (1989) 3;
(r) J.P. Issa, D. Lloyd, E. Steliotes, C.S. Bennett, Org. Lett. 15 (2013) 4170;
(s) P. Acharya, K.N. Baryal, C. Reno, J. Zhu, Carbohydr. Res. 448 (2017) 103;
(t) K.N. Barayl, J. Zhu, Org. Lett. 17 (2015) 4530;
(u) K.N. Barayl, D. Zhu, X. Li, J. Zhu, Angew. Chem., Int. Ed. 52 (2013) 8012;
(v) P.L. Durette, T.Y. Shen, Carbohydr. Res. 81 (1980) 261.

[15] A. Talla, B. Driessen, N.J.W. Straathof, L. Milroy, L. Brunsveld, V. Hessel, T. Noel, Adv. Syn. Cat. 357 (2015) 2180.

[16] (a) S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N.V. Tkachenko, H. Lemmetyinen, J. Am. Chem. Soc. 126 (2004) 1600;
(b) A.C. Benniston, K.J. Elliott, R.W. Harrington, W. Clegg, Eur. J. Org. Chem. (2009) 253;
(c) A. Joshi-Pangu, F. Léveque, H.G. Roth, S.F. Oliver, L. Campeau, D.A. Nicewicz, D.A. DiRocco, J. Org. Chem. 81 (2016) 7244.

[17] The proposed preference of oxidizing thiols over alkenes relies on their differences in reduction potentials.