Organic LETTERS

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Visible-Light-Driven Photocatalytic Initiation of Radical Thiol−Ene Reactions Using Bismuth Oxide

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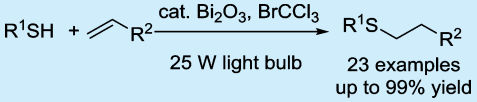
Supporting Information

ABSTRACT: A nontoxic and inexpensive photocatalytic initiation of anti-Markovnikov hydrothiolation of olefins using visible light is reported. This method is characterized by low catalyst loading, thereby enabling a mild and selective method for radical initiation in thiol−ene reactions between a wide scope of olefins and thiols.



Organosulfur compounds are widely present in nature and play important roles in many biological structures and functions.[1,2] Sulfur containing functional groups such as thioether, thioester, and disulfide are found in a number of natural products, for example the disulfide depsipeptide FK228 (romidepsin, anticancer);[3] the thioester depsipeptide largazole (anticancer);[4] and pharmaceutical agents such as ranitidine (Zantac, antiulcer),[5] NCH-31 (antitumor),[6] and the cyclic tetrapeptide disulfide SCOP (HDAC inhibitor) (Figure 1).[7]

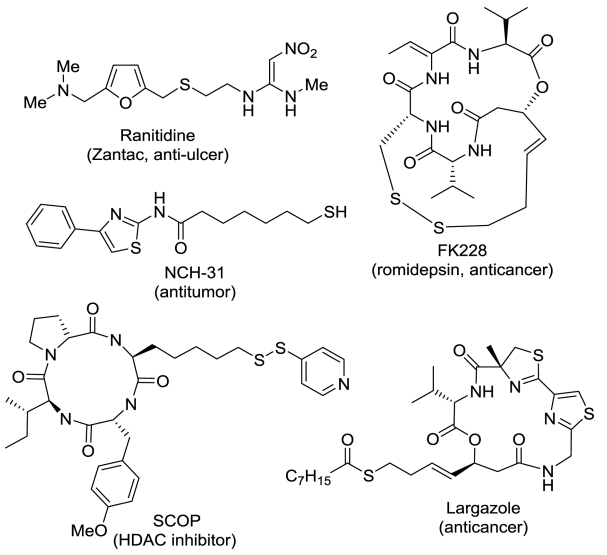


Figure 1. Bioactive sulfur-containing compounds.

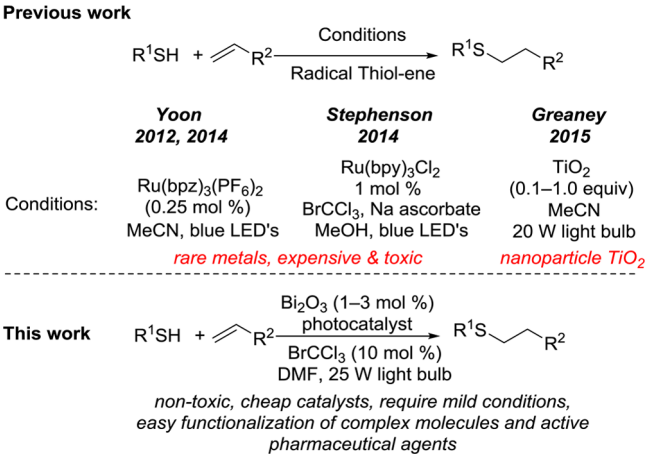
Disulfide-containing linkers are now used in antibody−drug conjugates (ADCs), which are used as targeted cell-based immunotherapeutics.[8] Lastly, organosulfur compounds commonly serve as useful synthetic intermediates, with applications in chemical biology, medicinal, and polymer chemistry.[1,2]

A common way to construct carbon−sulfur bonds is via the thiol−ene reaction, a prototypical "click reaction" that effects the anti-Markovnikov radical addition of thiol across non-activated carbon−carbon double bonds.[9] The high efficiency and orthogonality of thiol−ene chemistry has led to increased utility in polymer functionalization, macromolecular synthesis, biological applications, and functionalization of biomaterials.[10]

Growing concerns about the environment and energy use have spurred extensive efforts to make chemical processes more sustainable and "green". Examples include employing sunlight or low energy visible light to promote reactivity and performing synthetic transformations without the use of rare, expensive, and potentially toxic elements, especially in the pharmaceutical industry.[11]

Pioneering work by Yoon[12] and Stephenson[13] on radical thiol−ene coupling of alkenes and thiols (Scheme 1) using visible-light-absorbing ruthenium polypyridyl complex ($Ru(bpz)_3^{2+}$ and $Ru(bpy)_3Cl_2$) photocatalysts constitutes a striking development of chemical transformations promoted by low-cost energy.[14] However, both methodologies require the use of

Scheme 1. Visible light-photoredox radical thiol−ene reaction



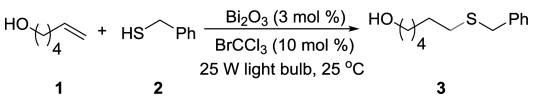
Received: September 30, 2015

DOI: 10.1021/acs.orglett.5b03184
Org. Lett. XXXX, XXX, XXX−XXX

rare, expensive, and toxic metals (Scheme 1). More recently, Greaney and co-workers reported the use of the naturally abundant and nontoxic metal oxide TiO_2 for thiol−ene coupling, but the protocol requires a nanoparticulate form of TiO_2 and the substrate scope was limited (Scheme 1).[15] We were interested in finding an alternative photoredox catalytic initiation to promote hydrothiolation, one that is not only mild, cheap, and nontoxic but also more efficient and suitable for late-stage functionalization of biologically relevant molecules. Upon perusal of the literature, we were inspired by the work of Pericàs and co-workers in which inexpensive and nontoxic bismuth-based materials were used as photocatalysts for the direct asymmetric alkylation of aldehydes.[16] Based on this precedent, we sought to develop a mild photocatalytic method for alkene hydrothiolation utilizing visible light activation and a bismuth oxide photocatalyst. It is worth noting that during our work in this area Pericàs reported the use of the bismuth oxide photocatalysts for the atom transfer radical addition (ATRA) reaction of organobromides to alkenes.[17]

We first set out to determine if bismuth oxide (Bi_2O_3) would catalyze the visible light initiated radical thiol−ene reaction and optimize the reaction conditions (Table 1). Initial investigation

Table 1. Bismuth Oxide Photocatalytic Initiation of Radical Thiol−Ene Reaction: Optimization Studies[a]



1 2 3

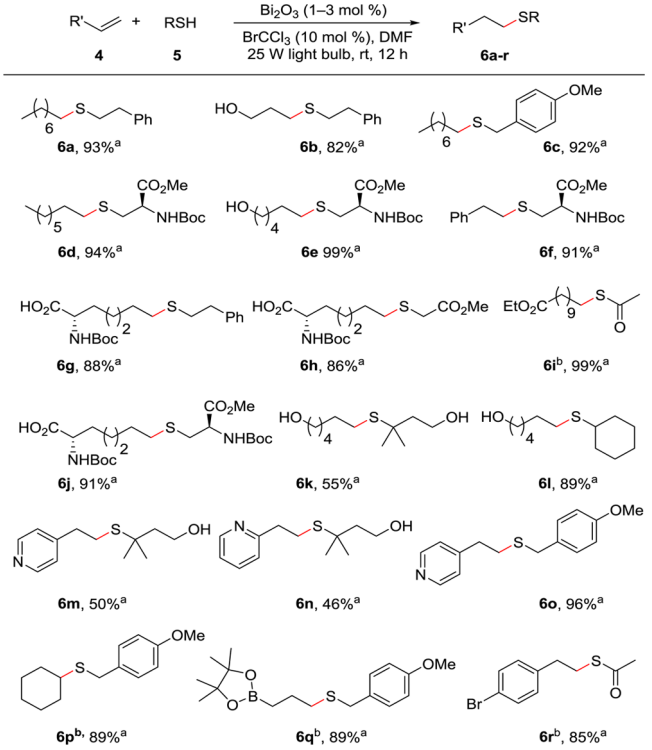
entry	condition	time (h)	solvent	conv (%)[b]
1	0 mol % $BrCCl_3$	24	DMF	<5
2	5 mol % $BrCCl_3$	12	DMF	90
3	as shown	12	DMF	>95[c]
4	as shown	12	DMSO	>95
5	as shown	12	MeCN	37
6	as shown	12	MeOH	41
7	0 mol % Bi_2O_3/$BrCCl_3$	24	DMF	35
8	no light	24	DMF	0
9	1 mol % Bi_2O_3	12	DMF	>95[c]
10	1 mol % Bi_2O_3/sunlight	6	DMF	>95[d]
11	1 mol % Bi_2O_3/1 equiv of **2**	20	DMF	75[e]
12	1 mol % Bi_2O_3/2 equiv of **1**	20	DMF	66

[a]All reactions were performed on a 0.5 mmol scale, alkene (1.0 equiv), thiol (4.0 equiv), and solvent (0.7 mL). [b]Conversion of all reactions determined by NMR analysis of the crude reaction mixture. [c]91% isolated yield. [d]94% isolated yield. [e]55% isolated yield.

into the proposed Bi_2O_3 catalyzed thiol−ene reaction focused on the reaction of 5-hexen-1-ol **1** and benzyl mercaptan **2** (Table 1). Irradiation of the alkene and thiol in the presence of photocatalyst Bi_2O_3 (3 mol %) produced only poor conversion to the addition product after 24 h (Table 1, entry 1). However, we were delighted to find that addition of 5 mol % of a single electron acceptor bromotrichloromethane ($BrCCl_3$) provided the desired thioether **3** in excellent conversion (Table 1, entry 2) after 12 h. Utilization of $BrCCl_3$ to promote the generation of the thiyl radical was previously reported by Stephenson and co-workers.[13] It is presumed that the trichloromethyl radical generated from the photocatalyst abstracts the hydrogen atom of the mercaptan to give the electrophilic thiyl radical intermediates that undergo addition reaction with alkene **1** to give the desired thioether **3**. Control experiments highlighted the essential roles of the photocatalyst, $BrCCl_3$, and light in this transformation (entries 3, 7, and 8). The background reaction was observed in the absence of the bismuth photocatalyst and $BrCCl_3$ (entry 7) but in only 35% conversion after 24 h. Interestingly, the thiol−ene reaction proceeded highly efficiently under sunlight (entry 10). Importantly, lowering of the catalyst loading had no impact on the overall performance of this protocol (entry 9), but due to reaction operational simplicity, 3 mol % was utilized as the optimal catalyst loading. Stoichiometric thiol (entry 11) or excess olefin (entry 12) still afforded practical but much lower conversion.[18] Finally, an evaluation of solvents revealed that the reaction performed best in DMF and DMSO (entries 3−4).

With the optimized conditions in hand, we next sought to evaluate the scope of the reaction using a variety of thiols and olefins. As depicted in Table 2, a range of structurally diverse alkenes **4** and thiols **5** gave the desired thioether product (Scheme 2, **6a**−**6r**). Both aliphatic alkene and styrene

Scheme 2. Bismuth Oxide Photocatalytic Initiation of Radical Thiol−Ene Reaction: Representative Substrate Scope



[a]All reactions were performed on a 0.5 mmol scale, alkene (1.0 equiv), thiol (4.0 equiv) and solvent (0.7 mL). Shown are yields after chromatography. [b]1 mol % of photocatalyst used.

substrates possessing various functional groups (including pyridine-based heteroaromatics, alcohols, esters, carboxylic acids, Boc-protected amines, and boronic pinacol esters) react smoothly under the optimized reaction conditions to afford radical−thiolene adducts with the expected anti-Markovnikov regioselectivity in generally high yields. Interestingly, allyl boronic ester functionality was well-tolerated as exemplified by the preparation of the useful synthetic intermediate for Suzuki couplings **6q** in 89% yield.

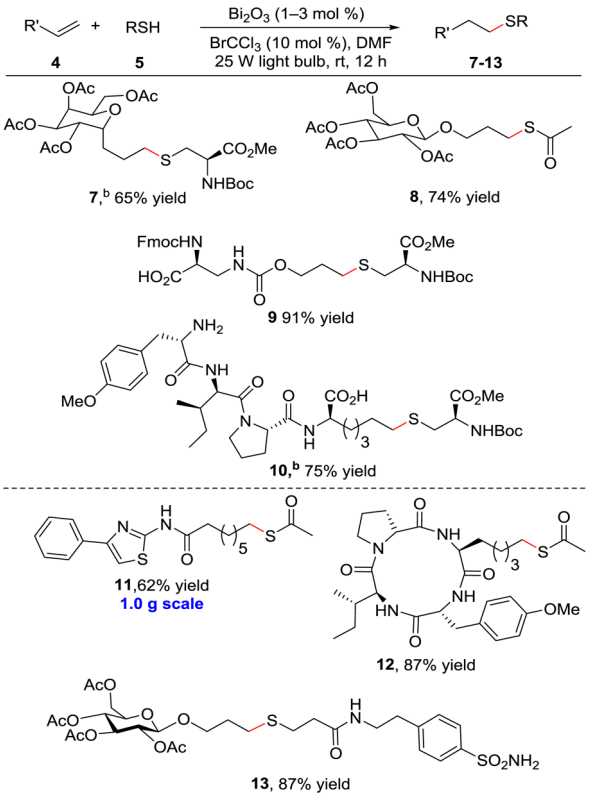
As shown in Scheme 2, we found that a broad range of thiol substrates readily participate as coupling partners in the radical

DOI: 10.1021/acs.orglett.5b03184
Org. Lett. XXXX, XXX, XXX−XXX

thiol−ene protocol. Alkyl (Scheme 2, **6a**, **6b**, and **6g**) and benzyl thiols (**6c**, **6q**, **6p**, and **6o**) all delivered the corresponding thioether products in good to excellent yields (82%−96% yield). Bulkier thiols such as cyclohexyl (**6l**) and tertiary thiols (**6k**, **6m**, and **6n**) gave the desired thiolene adducts in moderate to good yields (48%−89%). Thiol substrates with more acidic thiols such as methyl thioglycolate (**6h**), Boc-protected cysteine (**6d**, **6e**, **6f**, and **6j**), and acyl thiol (**6i** and **6r**) all proceeded smoothly in nearly quantitative yields.

Given the broad generality and operational simplicity shown in the scope of the photocatalytic initiation of the radical thiol−ene reaction, we were keen to explore the synthetic application of our methodology to late-stage diversification of advanced, highly functionalized, complex biomolecules and active pharmaceutical agents. As illustrated in Scheme 3, a variety of

Scheme 3. Late-Stage Diversification of Complex Biomolecules and Active Pharmaceutical Agents[a]

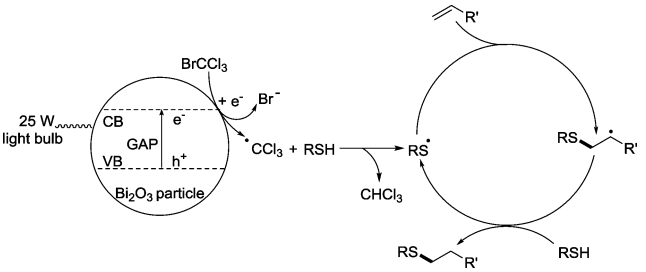


[a]Conditions: 4 (1.0 equiv), 5 (4.0 equiv) in DMF (0.7 M). Yields are of isolated product. [b]1 mol % of photocatalyst used

complex biologically relevant scaffolds readily undergo the hydrothiolation transformation to provide the useful glycochemistry substrates tetra-*O*-acetyl-pyran **7** and tetra-*O*-acetyl-*β*-D-glucopyranoside **8**, Fmoc-protected amino acid **9**, and linear tetrapeptide **10** in 65%, 74%, 91%, and 75% yields, respectively. Notably, the reaction is compatible with *N*-Fmoc-protected amino acid basic and acidic groups, with no effect on the rate or overall performance of the protocol. Additionally, we applied our protocol to the synthesis of the *S*-acetyl protected precursor to NCH-31 (a potent antitumor agent) **11**, the cyclic tetrapeptide SCOP (a potent HDAC inhibitor) **12**, and the glycosyl sulfonamide **13** (a potent carbonic anhydrase (hCA IX and hCA XII) inhibitor (Scheme 3). This demonstrated that a variety of complex drug-like molecules could be accessed via late-stage functionalization by employing this mild technology.

Proposed mechanistic details for the photocatalytic initiation of the radical thiol−ene reaction are depicted in Scheme 4. It

Scheme 4. Proposed Mechanism for Bismuth Oxide Thiol−Ene Reaction



has been established that irradiation of bismuth oxide with visible light leads to the creation of positive holes (h^+) on the surface of the semiconductor due to the photoexcitation of electrons from the valence to the conduction band.[16,17] We propose here that the photoexcited electrons induce reductive cleavage of the bromotrichloromethane to generate trichloromethyl radicals that readily abstract the thiol hydrogen atom producing the thiyl radical, which in turn initiates the radical thiol−ene process.[12]

In summary, we have developed a mild, inexpensive, and nontoxic visible light-driven photocatalytic initiation system of hydrothiolation of alkenes using Bi_2O_3 with wide functional group compatibility. This methodology lent itself in the late-stage hydrothiolation of useful complex biomolecules. To highlight the robustness of this technology, we achieved the synthesis of relevant pharmaceutical agents. Further biological application of this methodology is in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03184.

Complete preparatory and analytical data for all new compounds (PDF)

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are very grateful to Joe Tucker and Steve Wright, Pfizer Inc, for helpful conversations. This paper is dedicated to Professor Amos B. Smith, III, Rhodes-Thompson professor of chemistry at the University of Pennsylvania, for his recent 2015 Allan R. Day award.

DOI: 10.1021/acs.orglett.5b03184
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(18) To cover the broad substrate scope, 4 equiv of thiol were used throughout the following investigation.

DOI: 10.1021/acs.orglett.5b03184
Org. Lett. XXXX, XXX, XXX−XXX