Photoinitiated Thiol-Ene “Click” Reaction: An Organocatalytic Alternative

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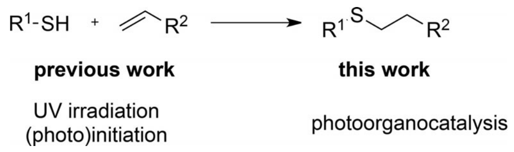
Abstract: The thiol-ene coupling (TEC) reaction has attracted a lot of scientific attention during the last years, particularly in the fields of polymers, materials and more recently in drug design. The combination of organocatalysis and photocatalysis has enabled the development of an efficient synergistic protocol for the addition of various thiols to a plethora of olefins. Utilizing phenylglyoxylic acid as the catalyst-initiator and common household bulbs as the light source, we report an organocatalytic photoinitiated TEC reaction showing exceptional tolerance in the presence of various functionalities, untangling previously unsolved problems.

Keywords: click chemistry; green chemistry; organocatalysis; photocatalysis; thiol-ene reactions

Introduction

Firstly reported by Posner in 1905,[1] the radical addition of thiols to olefins has emerged as one of the most important methods for the construction of carbon–sulfur bonds. The efficacy, atom economy and regioselectivity of this process fulfil the “click-chemistry” concept,[2] with applications in bioorganic chemistry,[3] polymer science[4] and pharmaceutical chemistry.[5] In the latter case, a variety of sulfur-containing pharmaceutical agents and natural products exist, like Zantac[5c] and romidepsin.[5d] In most cases, the reaction is promoted by either an expensive UV lamp or a radical initiator, but side-products often occur in the presence of various functionalities due to uncontrollable radical pathways. Yoon[6] and Stephenson[7] reported the use of transition metal complexes as efficient catalysts for the thiol-ene reaction in the presence of blue LED irradiation. More recently, titanium nanoparticles have been combined with visible light to promote the TEC reaction.[8] However, as presented in the literature, there are limiting factors, such as poor yields or selectivities in certain classes of substrates or high reagent ratios that undermine the generality of the TEC reaction. More recently, Renaud and coworkers reported a solution to the AIBN-promoted glycoside thiol-ene reaction *via* a catechol/BEt_3 repair mechanism, highlighting the need for improvement in the field.[9] In an effort to move a step forward, we present herein an organocatalytic photoinitiated TEC reaction, utilizing a catalytic protocol rather than a stoichiometric one (Scheme 1). During the last decade, photoredox catalysis has emerged as a viable solution for longstanding problems.[10] In general, expensive transition metal catalysts are employed, which have the advantage of our being able to tune their electronic properties through ligand manipulation. A far more cheaper approach was the introduction of photoorganocatalysis.[11] We have recently diverted our attention to the development of an organocatalytic protocol for various radical transformations that is easy to operate and enhances the concept of green chemistry.[12]

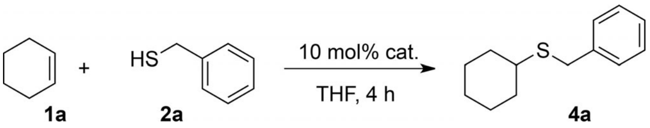


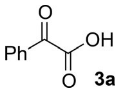
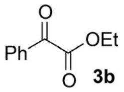
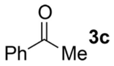
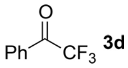
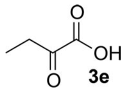
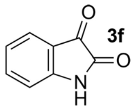
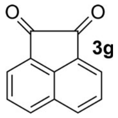
Scheme 1. Photoorganocatalytic TEC reaction.

Results and Discussion

In an effort to expand this protocol, we initially investigated the reaction between cyclohexene (**1a**) and benzyl mercaptan (**2a**). In the absence of catalyst, the reaction did not proceed (Table 1, entry 1). Phenyl-

Table 1. Catalyst optimization.

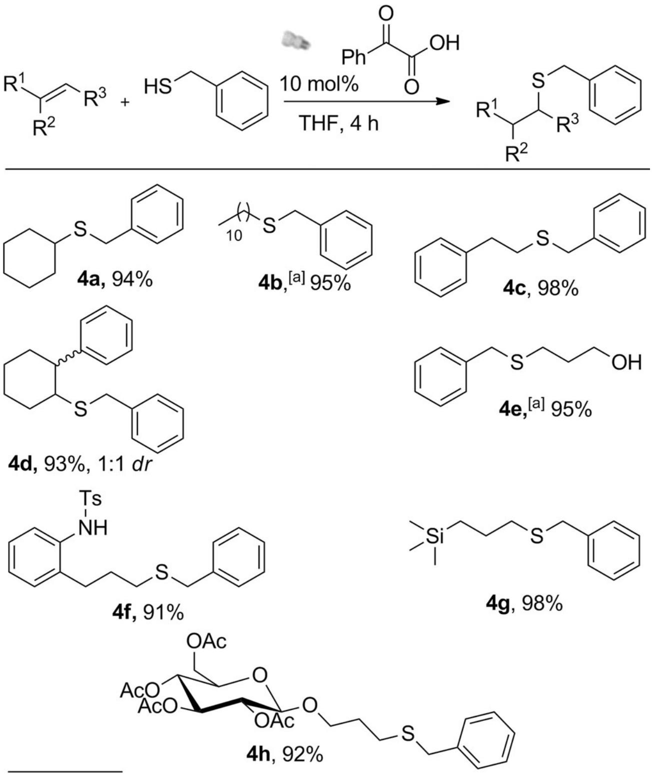


Entry	Catalyst	Yield [%][a]
1	–	8
2		100 (94)
3		66
4		55
5		17
6		12
7		15
8		33

[a] Yield determined by ^{1}H NMR spectroscopy, isolated yield in parenthesis.

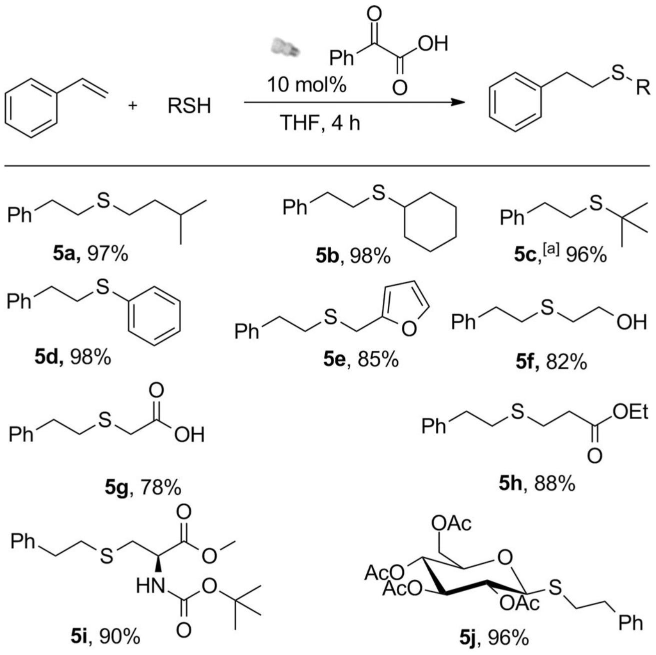
glyoxylic acid (**3a**) outperformed all the carbonyl compounds (**3a**–**g**) tested and proved to be the most suitable photoorganocatalyst providing the product in quantitative yield (Table 1). The absorbance spectra of compounds **3a**–**g** are included in the Supporting Information. Compounds that behave badly as catalysts (**3d**–**f**) lack any significant absorbance above 210 nm. Compounds with poor to moderate catalytic activity (**3b**, **3c** and **3g**) show an absorbance maximum around 250 nm with smaller shoulders at higher wavelengths (UVA or UVB). In addition to an absorbance maximum around 250 nm, phenylglyoxylic acid (**3a**) features both an aromatic group and a carboxylic moiety that stabilize (better than acetophenone **3c**) the diradical produced after irradiation. Extensive optimization showed that THF was the best solvent for this protocol.[13] Importantly, a low olefin-to-thiol ratio of 1:1.3 was proved to be adequate for the completion of the reaction. Moreover, the reaction can be carried out in water leading to an excellent yield (93% isolated yield), making this protocol suitable for green applications.[13] Taking into account the above absorbance data and phenylglyoxylic acid's triplet energy (62 kcal/mol in non-aqueous solvents),[14] household lamps could be successfully replaced by sunlight (September 2, 2015, 11:00–15:00, Athens, Greece, 37.97° N, 23.72° E), leading to a similarly excellent yield.[13] This was feasible and will be discussed extensively below regarding the mechanism of this protocol.

Having established the optimum reaction conditions, we turned our attention in the exploration of the substrate scope of the reaction. First, a series of olefins was tested for their reaction with benzyl mercaptan (Scheme 2). When decene (an aliphatic olefin) was utilized, the corresponding thioether was isolated in excellent yield in just 2 hours (**4b**). Styrene provided the product in quantitative yield, while the trisubstituted olefin 1-phenylcyclohexene was also well tolerated (**4c**, **4d**). Introducing an alcohol or an amine group did not affect the outcome of the reaction and the corresponding thioethers were isolated in high yields (**4e**, **4f**). In the same manner, allyltrimethylsilane was also employed (**4g**). In all the above cases, 1.3 equivalents of thiol were employed. One of the main disadvantages of the existing methodologies involve low-yielding reactions for weak C–H bonds (allylic or benzylic fragments),[9,15] especially in glycochemistry,[16] thus requiring a large excess of the thiol (up to 15 equiv.).[17] Our photoorganocatalytic protocol provides an excellent solution to this end. *O*-Allyl glycopyranose thioether **4h** was isolated in excellent yield and no competing reactions were observed, in



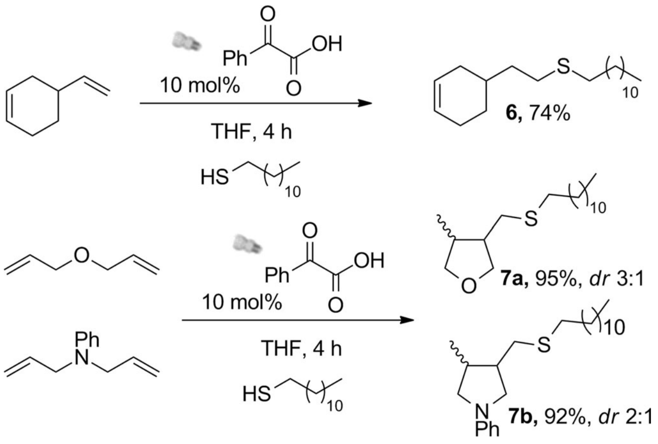
[a] Reaction time 2 h.

Scheme 2. Olefin substrate scope.



[a] Reaction time 20 h.

Scheme 3. Thiol substrate scope.



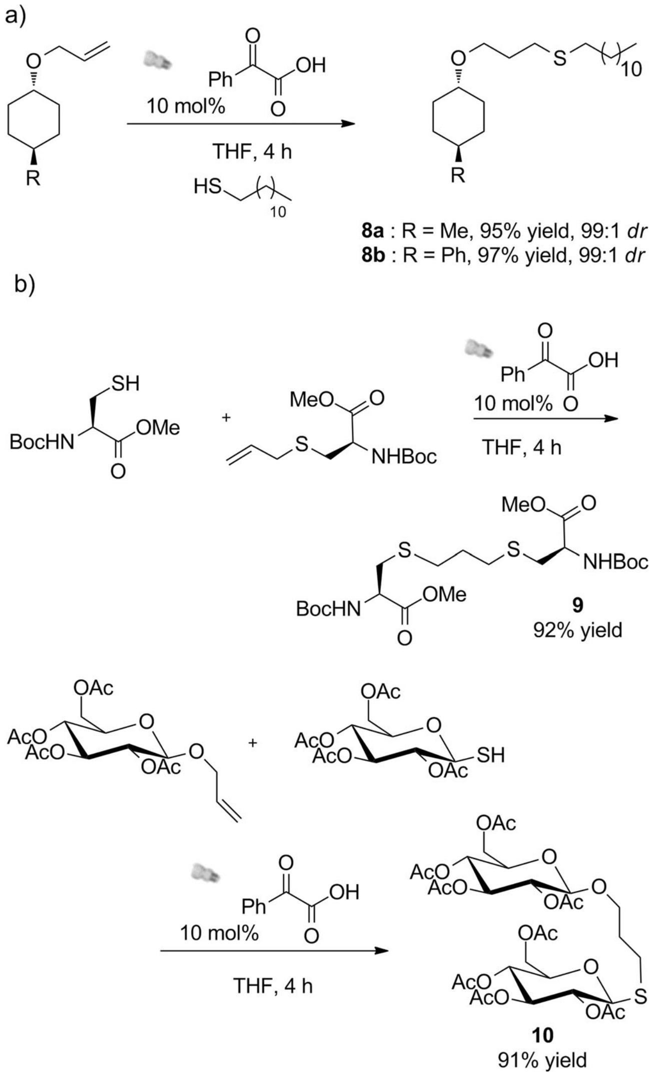
Scheme 4. "Difficult" TEC reactions.

contradiction to literature reports, where poor yields (around 25%) were established for TEC reactions of allyl glycosides with thiols.[9,18] In order to expand the substrate scope of our protocol, we tested a wide variety of thiols with styrene (Scheme 3). Primary and secondary thiols were well tolerated affording the corresponding products in high yields (**5a**, **5b**). An excellent yield was also observed when *tert*-butyl mercaptan was utilized, however, a longer reaction time was required for the reaction to reach completion (**5c**). Moreover, thiols bearing an aromatic ring were successfully tested and high yields were established (**5d**, **5e**). In addition, we tested thiols possessing various functional groups, such as a hydroxy, carboxyl or ester group and the products were afforded in high yields (**5f**–**h**). This method also found application in the modification of cysteine and may find great application in late-stage peptide functionalization (**5i**). Finally, when 1-thio-β-D-glucose tetraacetate was utilized, the corresponding product was afforded in very high yield, highlighting again the potential of this methodology in glycochemistry (**5j**).

Having in hand a broad substrate scope, we turned our attention in accomplishing "difficult" TEC reactions, demonstrating an organocatalytic alternative to a number of remaining challenges as precedent research illustrates.[9] Dodecanethiol was initially tested with 4-vinylcyclohexene (Scheme 4). A preference for the terminal olefin was observed and the product was isolated in 74% yield. Moreover, when diallyl ether or *N*,*N*-diallylaniline were utilized, the corresponding tetrahydrofuran **7a** and *N*-protected pyrrolidine **7b** were afforded in 95% and 92% yields, respectively.

Next, we explored the TEC reaction between dodecanethiol and two *trans*-allyl ethers (Scheme 5a). Previous reports underline the "difficulty" that such substrates show under thermal radical conditions, often resulting in low yields, since the allyl radical produced leads to a number of unwanted side-reactions.[9] Herein, an excellent yield with untouched diastereoselectivity was observed. Moreover, in an effort to explore peptide, as well as glycoside, functionalization, we demonstrated the linkage of two amino acid derivatives and two monosaccharide units by implementing our methodology (Scheme 5b). In the former case, two cysteine derivatives were linked together forming a bis-thioether and in the latter, two glycopyranose derivatives formed compound **10**.

Mechanistic studies were carried out in order to support the organocatalytic photoinitiated pathway of the reaction. The reaction between cyclohexene and benzyl mercaptan was left stirring as follows: one hour in the presence of bulb light and one hour in absolute dark (On-Off experiment) (Figure 1). In the absence of light, the reaction did not progress, thus one could assume that the radical intermediate of the reaction is quickly quenched when the light is off. Both the light and the photocatalyst are absolutely essential for the reaction to reach completion. Spectroscopic experiments were performed in order to shed more light to the reaction mechanism. UV absorption spectra in THF (using concentrations similar to those of the reaction mixture) of each individual reactant under the reaction conditions showed interesting results (Figure 2). Decene and thiol gave similar absorption spectra with low absorption below 300 nm, whereas phenylglyoxylic acid showed increased absorption starting in the early visible wavelength area (Figure 2), which can explain why the reaction can be performed utilizing household lamps and under direct sunlight.



Scheme 5. More "difficult" TEC reactions.

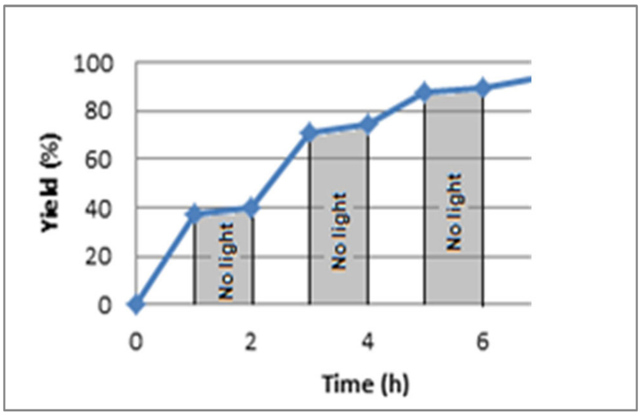


Figure 1. An "On-Off" mechanistic experiment.

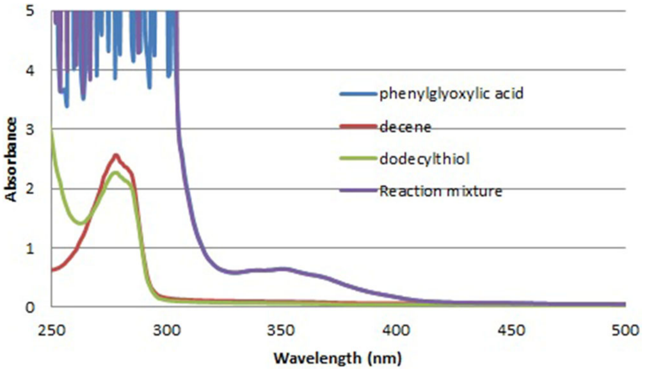


Figure 2. UV/Vis absorption spectra of thiol (0.1 M), decene (8×10^{-2} M), phenylgyoxylic acid (9×10^{-3} M) and the reaction mixture recorded in THF.

In a recent report, Cismesia and Yoon challenged the ability of a light-dark experiment as the sole evidence for a photocatalytic closed cycle mechanism versus a chain propagation cycle.[19] In that elegant contribution, the authors argued that since the typical lifetime of a radical chain process is rather short, the termination of the chain propagation during the dark time could be faster (and could occur for instance with the catalyst) and thus, conversion stops due to this termination. They presented the use of quantum yield as a useful tool for identifying such occurrences and demonstrated its use in three different examples (in all examples, conversion ceased during the dark period of the light-dark experiment).[19] If a closed catalytic cycle is involved, a maximum theoretical quantum yield (Φ) of 1 is expected (every photon absorbed by the photocatalyst produces a molecule of the product, whereas if non-productive pathways are involved, the quantum yield will decrease). On the contrary, a quantum yield of $\Phi \gg 1$ would mean a chain propagation process, since one-photon induced initiation would lead to multiple molecules of the product.[19] We began our studies by calculating the photon flux of our spectrophotometer utilizing potassium ferrioxalate, since it constitutes a well-established actinometer.[19,20] Taking these data into consideration, a photon flux of 4.29×10^{-10} einstein s^{-1} was calculated for 248 nm.[13] Then, the photocatalytic reaction of **1b** with dodecythiol using **3a** (10 mol%) as the catalyst was performed in the spectrophotometer for 1 h. Afterwards, the yield of the reaction was calculated *via* ^{1}H NMR. Thus, the quantum yield of the reaction was calculated by dividing the moles of the product formed by the einsteins of photons consumed, leading to a quantum yield of 188.[13] This process was also repeated for various wavelengths (Figure 3). In all cases, quantum yield values indicate propagation ($\Phi \gg 1$), but noteworthy the quantum yield of the reaction shows a maximum in the visible light area, which is in agreement with the reaction taking place under sunlight. This also leads us to assume that a chain nature of the reaction is followed, and under dark reaction conditions, the chain propa-

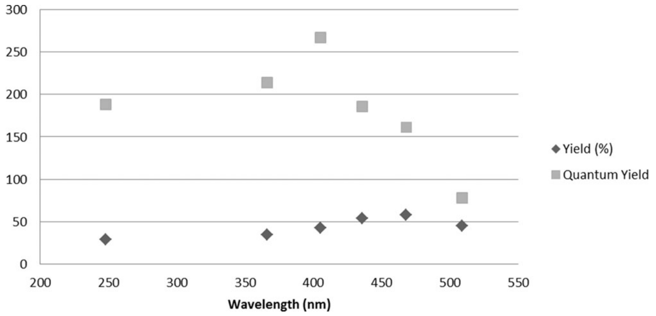


Figure 3. Yield (%) and quantum yield of the reaction between decene and dodecyl thiol utilizing phenylglyoxylic acid as the catalyst at various wavelengths.

gation terminates. Overall, a chain propagation mechanism is dominant. Thus, initially and upon irradiation, phenylglyoxylic acid *via* a HAT process affords the first thiyl radical. Addition of this radical to the alkene affords a new radical species, which propagates *via* a chain mechanism for the reaction.

Conclusions

In conclusion, a simple, cheap and efficient organocatalytic photoinduced protocol was developed and successfully applied to the TEC reaction between a wide variety of olefins and thiols. Bypassing the need for transition metal complexes, thermal (photo)initiators and stoichiometric additives, this method may find application in the field of peptide and glycoside modification, presenting functional group tolerance. Further applications of this protocol are currently under investigation.

Experimental Section

General Procedure

To a glass vial with a screw cap containing phenylglyoxylic acid (8 mg, 0.05 mmol) in THF (1 mL), alkene (0.50 mmol) and thiol (0.65 mmol) were added consecutively. The vial was sealed with a screw cap and left stirring under household bulb irradiation (2×60 W household lamps, see the Supporting Information) for 2–4 hours. The reaction progress can be monitored by GC-MS. After completion of the reaction, the product was isolated by flash silica chromatography of the crude mixture.

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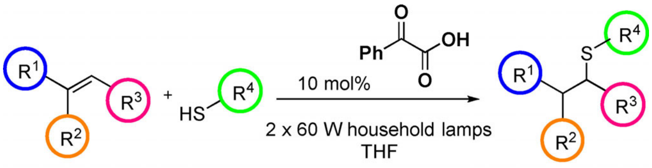

photoorganocatalytic repair of TEC reaction

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