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Stereoselective Synthesis of 3,4-Di-substituted Mercaptolactones via Photoredox-Catalyzed Radical Addition of Thiophenols

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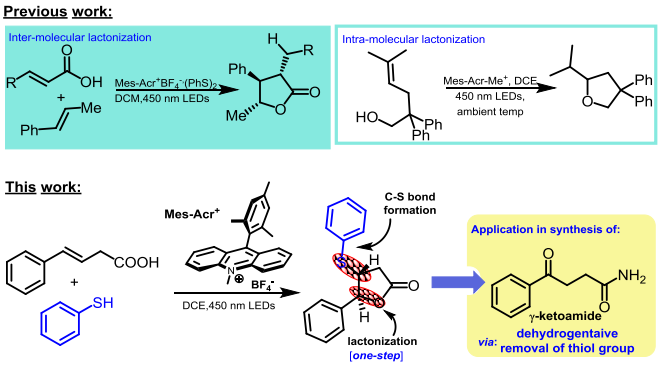
ABSTRACT

A visible light mediated radical addition of thiophenols on 4-phenylbut-3-enoic acids to give diastereoselective synthesis of 3,4-disubstituted γ-lactones is reported. The reaction precludes the conventional prerequisite of conjugate addition. Furthermore, the lactones were successfully utilized in the synthesis of γ-ketoamides.

1. Introduction

Sulfur-containing compounds comprised as much as one-fifth of the 200 most-prescribed pharmaceutical products in 2011.[1] The classic way to introduce a sulfur group on an alkene is via Michael addition,[2] which makes their addition on the non-conjugated system challenging. In this regard, thiyl radicals easily obtainable from corresponding thiols or disulfides can trigger a diverse range of reactions like thiol-ene coupling reactions, addition of thiols to alkynes, the addition of sulfonyl chlorides, decarboxylative additions of amino-acids via Giese reaction, photo-oxygenation, inter-molecular cyclizations, addition of alkyl halides and atom transfer reactions.[3] The addition of thiyl radicals on unsaturated systems like alkenes, alkynes, isonitriles and thiocarbonyl generally follow the basic principle of Markovnikov's addition. However, recently the ability of PhSH to produce thiyl radical has been very effectively utilized in the anti-Markovnikov hydrofunctionalization reactions of alkenes,[4] wherein they act as hydrogen atom transfer (HAT) catalysts. Though their application as HAT catalysts has made rapid in roads, it's the addition of thiols on the double bonds under given conditions, which remains largely unexplored.

This intrigued us to investigate the addition of thiyl radical on the 4-phenylbut-3-enoic acids as it would essentially rule out the conventional requirement of conjugated systems. Thus, in continuation of our interests on radical reactions,[5] herein we report a diastereoselective synthesis of 3,4-disubstituted-γ-mercaptolactones from 4-phenylbut-3-enoic acids via photoredox catalysis. Notably, γ-butyrolactones present one of the most explored class of compounds owing to their pervasive presence in myriad bioactive molecules.[6]

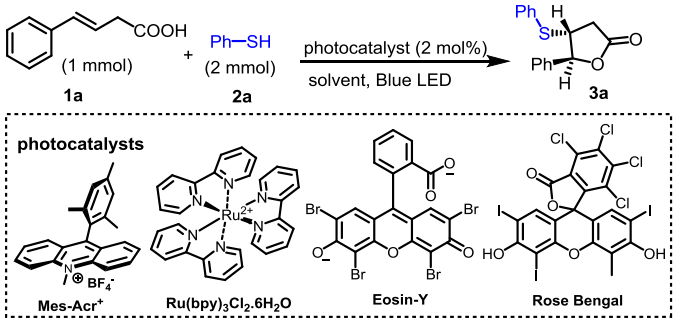


Scheme 1. Photoredox-catalyzed synthesis of lactones

Our studies initiated with the reaction of 4-phenylbut-3-enoic acid (**1a**) and thiophenol (**2a**) as model substrates. To our delight, the reaction of **1** and **2** in presence of blue LED (λ= 450-495 nm) using DCE (1,2-dichloroethane) as solvent and Mesityl acridinium ($Mes\text{-}Acr^{+}BF_4^{-}$) as photocatalyst led to the diastereoselective synthesis of **3a** in 78% yields (8:1 dr) as easily separable mixture of stereoisomers (Table 1, entry 1). The reaction was also found feasible in toluene, MeCN and H_2O, whereas other solvents such as DMSO, DMF, and MeOH resulted in no formation of product (Table 1, entries 2-7). Moreover, photocatalysts like $Ru(bpy)_3Cl_2$, Rose Bengal and eosin-Y were also found to catalyze the reaction albeit in

comparatively lower yields (Table 1, entries 8-10). Notably the reaction in absence of photocatalysts afforded the desired product in very low yields (Table 1, entry 11). Thus, the use of Mes-Acr$^+$BF$_4^-$ as photocatalyst in DCE irradiated with blue light was found to be the condition of choice.

Table 1. Optimization of the reaction conditions.[a]

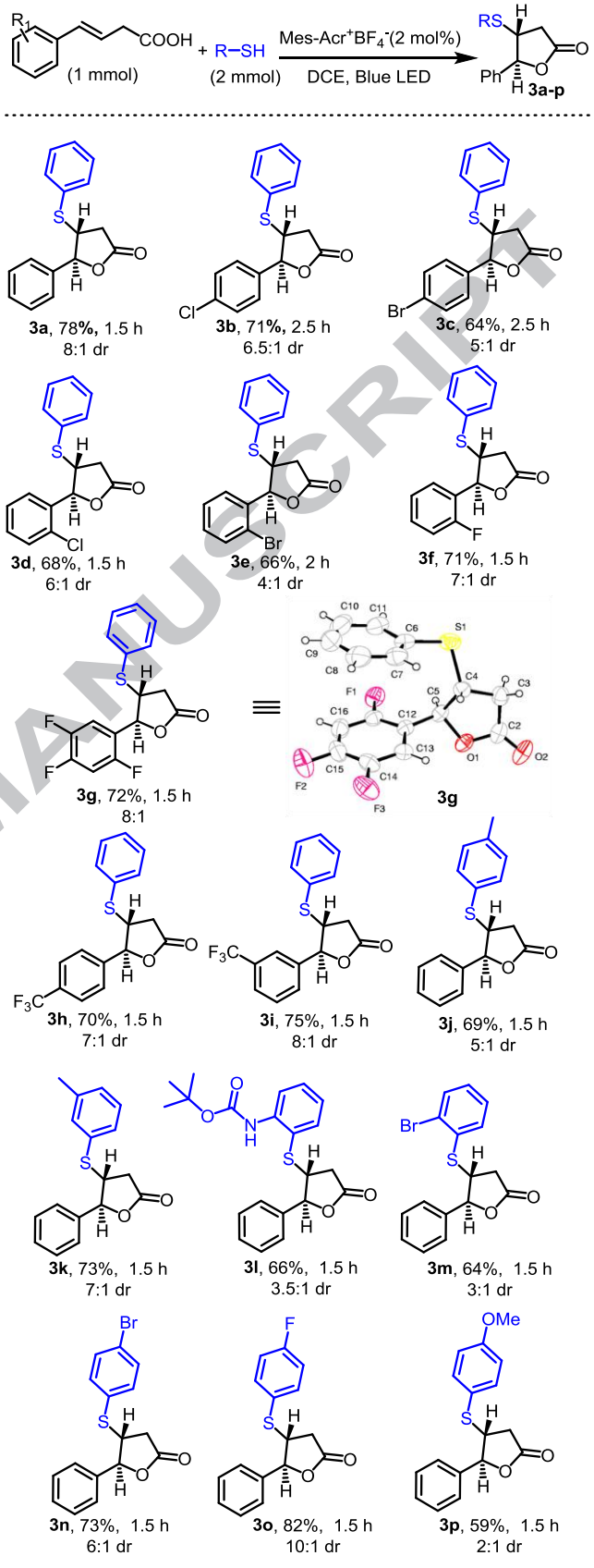


entry	photocatalyst	solvent	yield (%)[b]	diastereomeric ratio[c] (*anti:syn*)
1	Mes-Acr$^+$BF$_4^-$	DCE	78	8:1
2	Mes-Acr$^+$BF$_4^-$	DMSO	traces	-
3	Mes-Acr$^+$BF$_4^-$	DMF	traces	-
4	Mes-Acr$^+$BF$_4^-$	MeCN	45	-
5	Mes-Acr$^+$BF$_4^-$	Toluene	14	-
6	Mes-Acr$^+$BF$_4^-$	MeOH	traces	-
7	Mes-Acr$^+$BF$_4^-$	H_2O	33	-
8	Ru(bpy)$_3$Cl$_2$	DCE	49	-
9	Rose Bengal	DCE	51	7:1
10	eosin-Y	DCE	47	8:1
11	-	DCE	traces	-

[a]**1a** (1.0 mmol), **2a** (2.0 mmol), photocatalyst (2 mol%), solvent, Blue LED, 1.5 h. [b]Yields of major isomer **3** after column chromatography. [c]The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified reaction mixtures.

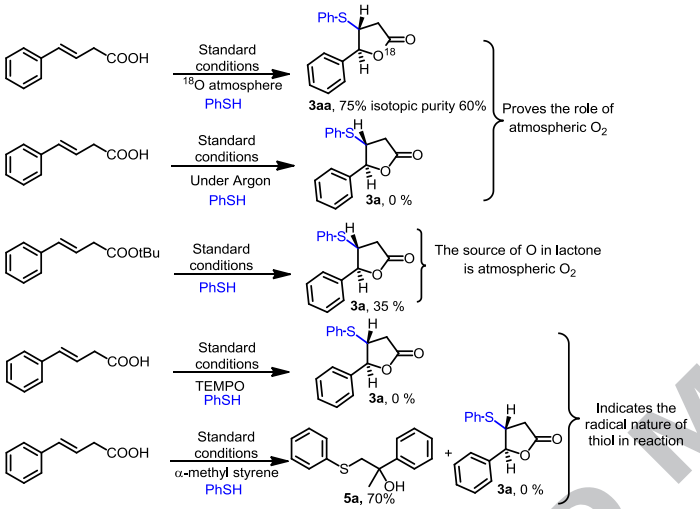
Having conditions optimized, the substrate scope was expanded to a range of 4-phenylbut-3-enoic acids and thiophenols (Scheme 2). The reaction of various halo substituted 4-phenylbut-3-enoic acids like 4-chloro, 4-bromo, 2-chloro, 2-bromo, 2-fluoro and 2,4,5-trifluoro 4-phenylbut-3-enoic acids with thiophenol gave **3b-g** in good yields and selctivity. Steric hindrance had no impact on the reaction yields, as reaction with ortho-substituted acids proceeded efficiently to give corresponding γ-lactones. The effect of electron-withdrawing functions was also investigated using *para* and *meta*-trifluoromethyl 4-phenylbut-3-enoic acids as substrates to get **3h-i** in 70 and 75 % yields respectively. The stereochemistry of the resulting products was established as *anti* by X-Ray crystallography (**3g**, scheme 2).

The scope of the reaction was also extended to different substituted thiophenols. The reaction worked well with electon-neutral (4-methyl and 3-methyl substituted), electron rich (2-amino and 4-methoxy substituted) and halo substituted (2-bromo, 4-fluoro, 4-bromo) thiophenols to give corresponding products **3j-p** in good yields and selectivity. These results demonstrate the versatility and tolerability of the present methodology with a range of substituted 4-phenylbut-3-enoic acids and thiophenols. Notably, the reaction with aliphatic thiols like hexane thiol did not yield the desired product, possibly due to less stability of aliphatic thiyl radical.



Scheme 2. Substrate scope with different acids and thiophenols.
[a]Yields shown are of major isomers **3** after column chromatography. [b]The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of unpurified reaction mixtures.

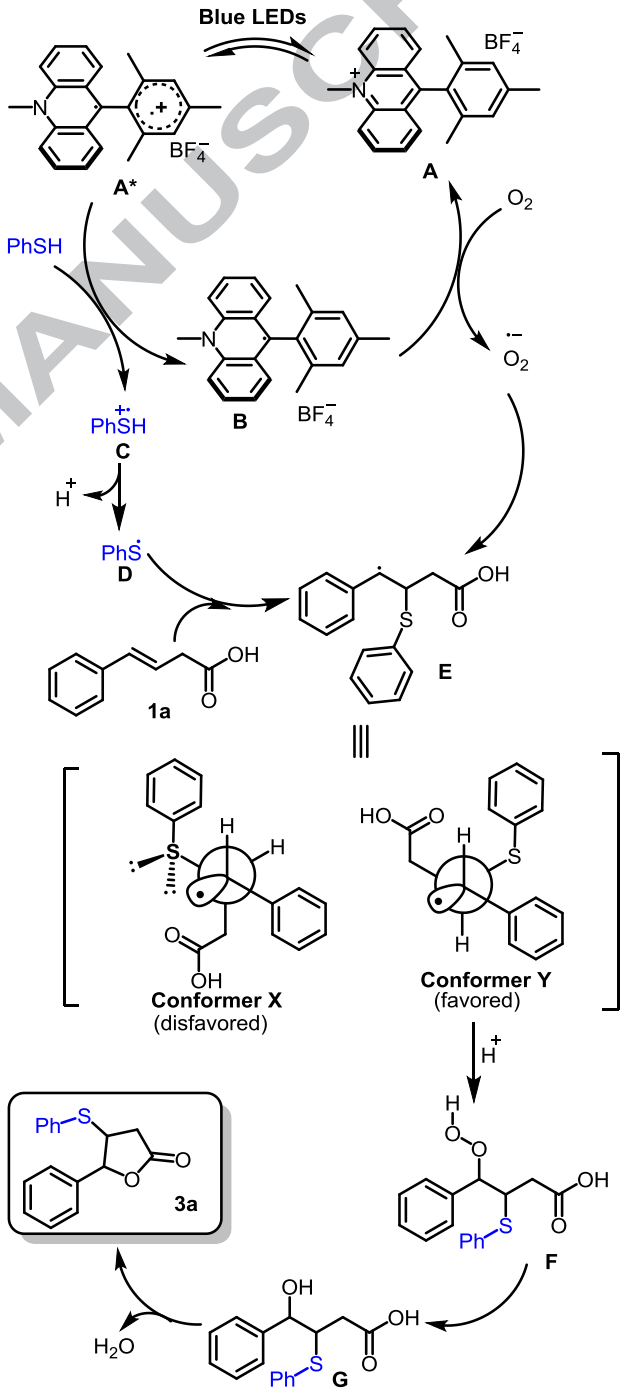
To obtain mechanistic insights, certain control experiments were performed (Scheme 3). In order to confirm the source of oxygen in the lactone ring, the reaction was carried under $^{18}O_2$ atmosphere using standard conditions. The incorporation of ^{18}O in the corresponding product evidenced by LC-MS studies implies that oxygen in the lactone is sourced from atmospheric oxygen. This is further corroborated by: (a) the reaction of ester, wherein, formation of product shows oxygen comes from atmospheric oxygen and not the acid moiety and (b) the reaction under inert conditions leading to no product formation. In order to ascertain, if the reaction proceeds through radical pathway we carried out the reaction in presence of radical quencher, TEMPO, which resulted in no product formation. Using, α-methyl styrene to trap the radical intermediate of thiophenol resulted in formation of β-hydroxy thiol-styrene adduct (Scheme 3).



Scheme 3. Control experiments.

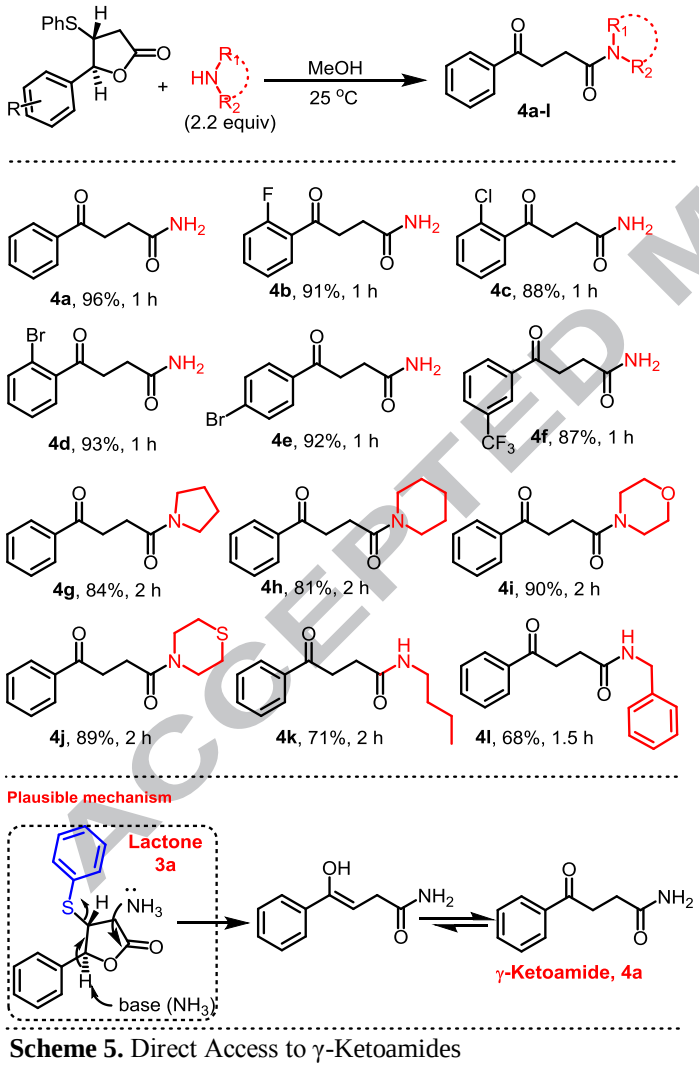
Based on literature reports and control experiments a plausible reaction mechanism is shown in Scheme 4. The photo-excitation of Mes-Acr$^+$BF4$^-$ (**A**) under blue LED results in the formation of short-lived transition state **A*** which receives an electron from thiophenol to generate the radical intermediate **B** and radical cation **C**.[14] The Mes-Acr$^+$BF4$^-$ **A** is regenerated from **B** via single electron transfer with atmospheric oxygen.[14,15] The radical cation C releases the proton to form relatively stable intermediate thiyl radical **D**, which adds to the 4-phenylbut-3-enoic acid to generate stable benzylic radical adduct **E**. The oxygen radical anion generated in-situ adds to the benzylic radical in presence of H^+ released by thiyl radical cation to produce a superoxide intermediate **F**.[16] The addition of molecular oxygen on sulfanyl radical *i.e.*, intermediate E on exocyclic system is well known to promote anti-addition.[3] In the present case the selective formation of anti-isomer can possibly be explained on the basis of conformer **Y**, which is also exemplified by crystal structure of **3g**. The stability of conformer **Y** (having gauche configuration) over conformer **X** (having staggered configuration) may be attributed to the electronic repulsions between radical and non-bonding electron pair on sulfur. The cleavage of peroxide to hydroxide with the subsequent loss of water molecule[17] and cyclization yields the final product **3a**.

Next, we contemplated the ring opening reaction of lactone **3a** with a simple nucleophile NH_3. To our surprise, the reaction of **3a** with aqueous NH_3 led to the ring opening of lactone as well as removal of thio moiety to produce γ-ketoamide, **4a** in 96% yields (Scheme 5). To the best of our knowledge the simultaneous ring opening as well as de-thiolization of thiolactones is not known. The method gives an easy access to γ-keto amides which otherwise require multi-step for their preparation. It would be pertinent to mention here that 1,4-dicarbonyl moiety is a key component of many bioactive molecules such as thiaplakortone A, lignans, and mitomycin C as well as versatile building block for the synthesis of various heterocyles such as furans, pyrroles and thiophenes by Paal-Knorr synthesis.[18,19] This has led to the development of copious method for their synthesis with most of the method relying on the reactions between two derivatives of carbonyl compounds. Examples include, conjugate addition of acyl anion equivalents to Michael acceptors, nucleophilic substitution of α-haloketones,[20] chain extension of 1,3-dicarbonyl compounds,[21] oxidative coupling of enolates[22] or alkenes,[23] and the addition of homoenolate equivalents to acid derivatives,[24] enolate heterocoupling[25] and more recently through radical addition.[26]



Scheme 4. Plausible mechanism

Despite the great successes achieved in the synthesis of 1,4-dicarbonyls, significant improvement is still in demand in terms of availability of starting materials, substrate scope, and functional group tolerance. This led us to examine its substrate scope with various substituted γ-lactones, which as expected afforded the facile formation of derivates **4a-f** in excellent yields. Next, we investigated the scope of various primary and secondary amines. The reaction of pyrollidine, piperidine, morpholine and thiomorpholine, gave corresponding products **4g-j** in excellent yields. The method was equally facile with n-butyl and benzyl amine resulting in the formation of corresponding products **4k-l** in good yields. The reaction is extendable to a diverse range of primary and secondary amines including those containing hetero-groups. Also, the presence of different function on aromatic ring sourced from acid had no impact on reaction yields. The formation of γ-ketoamide from **3a** can proceed either via hydride shift or proton abstraction, since we are using base, the reaction possibly proceeds via abstraction of acidic benzylic proton by the base (amine)[27] to remove thiophenol, followed by concomitant attack of amine on the carbonyl to give γ-keto amide **4a**.



Scheme 5. Direct Access to γ-Ketoamides

In summary, we have developed a visible light mediated strategy for the radical addition of thiophenols on 4-phenylbuten-3-oic acids leading to diastereoselective synthesis of 3,4-disubstiuted γ-lactones. The reaction features a one step C-S bond formation and cyclization as well as obviates the need of conjugate addition for introduction of sulfur group. Additionally we could expand the scope of reaction to the synthesis of γ-ketoamides viz., 1,4-dicarbonyls, wherein the ring opening is accompanied by C-S bond cleavage. The further reactivity and applicability of this reaction system is currently under investigation in our laboratory.

Acknowledgments

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Crystallographic data for the structure **3g** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-1557766.

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Supplementary Material

Experimental procedure, characterization data, ^{1}H and ^{13}C NMR of relevant compounds.

Highlights:

- A method for diastereoselective synthesis of 3,4-disubstituted γ-lactones
- Reaction features a one step C-S bond formation and cyclization.
- Stereochemistry established by X-ray crystallography.
- Lactones were successfully used in the synthesis of γ-ketoamides.

Tetrahedron Letters

Graphical Abstract

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Stereoselective Synthesis of 3,4-Di-substituted Mercaptolactones via Photoredox-Catalyzed Radical Addition of Thiophenols

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