Esterification of Carboxylic Acids utilizing Eosin Y as a Photoacid Catalyst

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Abstract: Esters represent a vital functional group in organic chemistry and are prominently featured in valuable molecules. Traditional approaches for ester synthesis from acids typically entail the use of strong acids and toxic activating agents. Photoacid-catalyzed organic synthesis has recently come to the fore in several important transformations accruing the benefits of acid-based reactions under mild conditions. In this context, a green and sustainable method for esterification is proposed wherein, Eosin Y is introduced as a multifunctional photoacid catalyst that can be activated with visible light and catalyze the esterification of carboxylic acids. The present strategy is fairly broad and applies to the esterification of cinnamic acids, *α*-keto acids, and phenyl propiolic acids. The scope of carboxylic acids and alkyl alcohols includes several examples and therefore provides various carboxylic ester building blocks of pharmaceutical interest. Elaborated mechanistic studies revealed that proton-coupled electron transfer (PCET) between Eosin Y and carboxylic acid might facilitate the formation of a transient ketyl radical. This ketyl radical would subsequently undergo coupling with alkyl alcohols, yielding carboxylic esters in good to excellent yields.

Keywords: *α*-keto ester • Cinnamate • Esterification • Eosin Y • Ketyl radical • Photoacid

Introduction

Esters are the most fundamental functionalities in organic chemistry considered to be invaluable for pharmaceutical chemistry and other chemical industries.[1] Amongst them, cinnamic esters and *α*-keto esters are widely prevalent in many biologically active compounds.[2] Traditional methods to synthesize esters from acids involve environmentally hazardous strong acids and toxic activating reagents.[3] To circumvent this, a few modified approaches in line with green and sustainable chemistry have been developed and hereby discussed in context to cinnamic esters and *α*-keto esters synthesis (Scheme 1).[4] Hou *et al.* reported the synthesis of methyl cinnamates by copper-catalyzed methyl carboxylation of styrenes,[5] however, this method required a two-step process to access cinnamic esters. Following this, copper-catalyzed strategies for the synthesis of *α*-keto esters have been reported by many research groups. For example, Jiao and co-workers reported an aerobic oxidative esterification of 1,3 diones with alcohol *via* C-C bond cleavage approach.[6] However, the formation of esters of benzoic acid as by-products badly impacted the atom economy of this method. Later, Song *et al.* utilized acetophenones,[7] whereas, Bai's group utilized *α*-diazo esters as substrates for the synthesis of *α*-keto esters.[8] Collectively, the requirement of metal catalysts, acids and bases, pre-synthesized, unstable, and shock-sensitive starting materials, high boiling solvents, and elevated reaction temperature impede the applicability of these methods.

Visible-light photocatalysis has emerged as a powerful tool for the generation of radicals and thus might provide an alternative to achieve a wide spectrum of reactions including the title reaction in a step economical way without the need to use stoichiometric amounts of reagents.[9] In this context, a visible-light-mediated method for esterification involving the oxidation of terminal alkynes using copper was also developed.[10]. Thereafter, Wan *et al.* developed a photocatalytic method employing Rose Bengal through the scissoring of C=C bond in enaminones[11] but this method suffers from the limitation of having a poor atom economy. Overall, a general, green, and sustainable method for esterification that involves the use of environmentally benign solvents, catalysts, and conditions is highly desired.

In the broader domain of visible-light photoredox catalysis, the recent advent of photoacids has led to many useful organic transformations.[12] Photoacids are molecules that have a higher proton-donating tendency in the excited state than in the ground state due to a respective change in the pKa value.[13] The first use of photoacids under visible-light has been reported by Toshima and co-workers wherein an organophotoacid-induced glycosylation was successfully attempted.[14] Later, Wang and co-workers explored glycosylation by using Eosin Y and other photoacid catalysts.[15] Since then, there have been a few excellent reports on the use of photoacids in Friedel-Craft's arylation of carbonyls,[16] acetal formation,[17] Minisci-type acylation of N-heteroarenes,[18] indane synthesis,[19] hydrodesulfurization of aryl thioethers[20] and glycosylation.[21] Structurally speaking, mostly, thioureas have been utilized as photoacids. In addition, naphthols, MEH, and disulfides also have acted as photoacid catalysts (Figure 1).

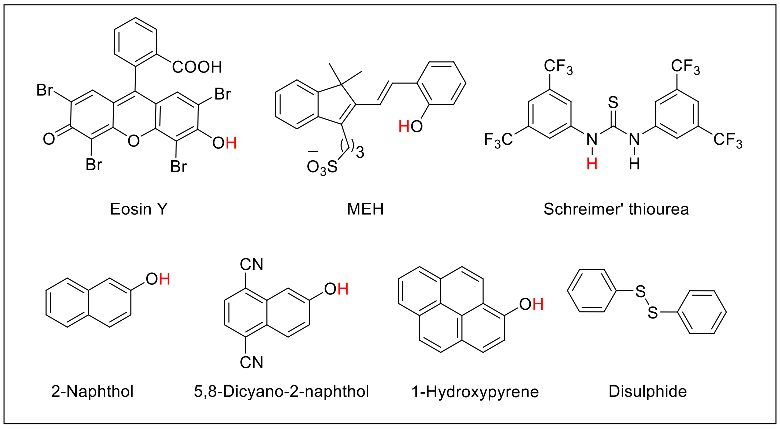
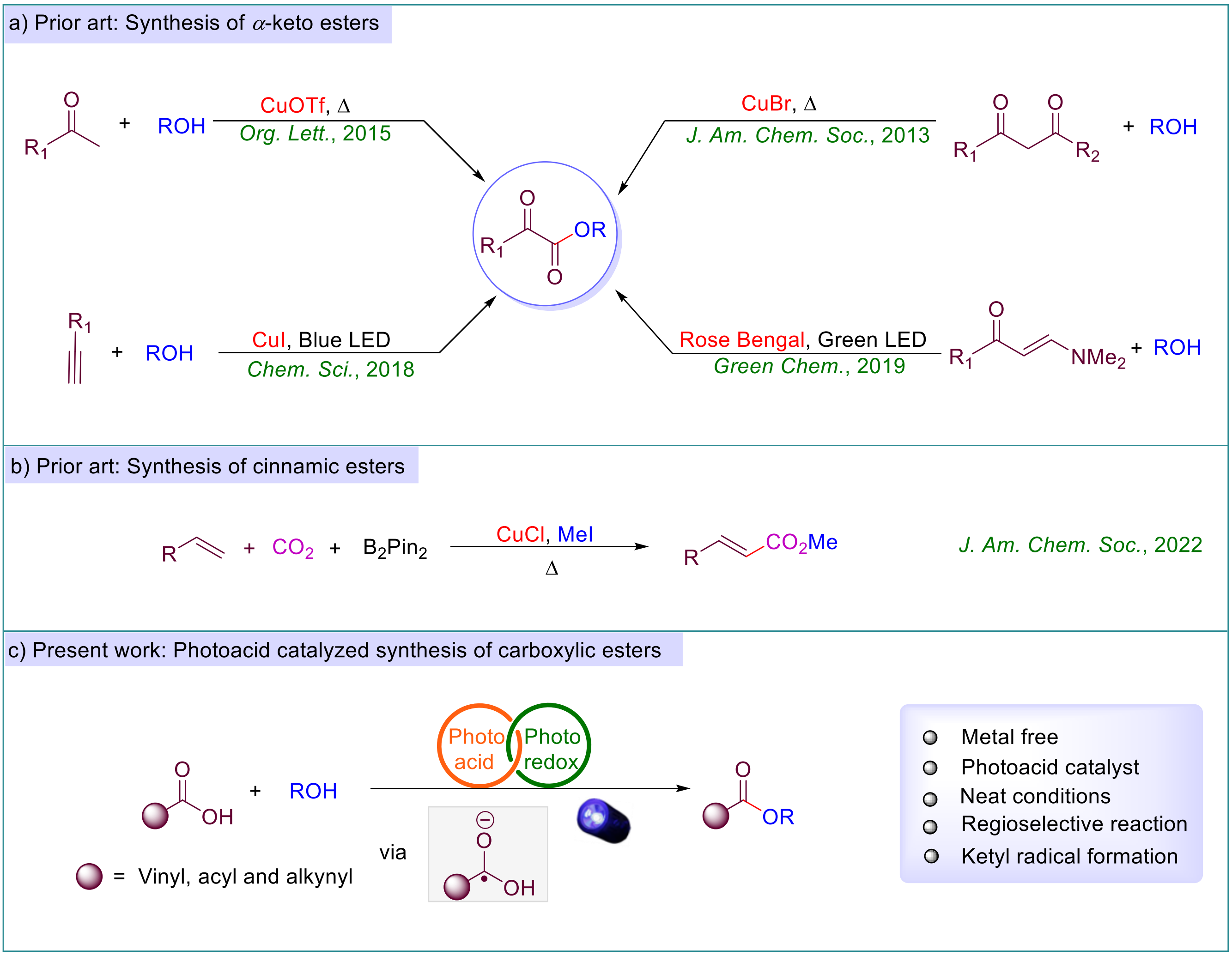


Figure 1: Structure of photoacid catalysts.

Based upon the above discussion and our interest in developing green and sustainable synthetic protocols,[22] we hypothesized that esterification of carboxylic acids can be achieved by the use of photoacids. We intended that a suitable photoacid, under visible-light irradiation, may protonate the acid and a concurrent SET may result in generating a ketyl radical of the acid. However, the challenge is the selective ketyl radical formation of the less reactive carboxylic acid function of the substrate. We believed that a process akin to PCET involving a photoacid may resolve this reactivity problem. Herein, we disclose an Eosin Y-catalyzed esterification of carboxylic acids such as α-keto acids, cinnamic acids, and phenyl propiolic acids (Scheme 1). Mechanistic studies reveal that esterification was achieved *via* reductive pathway. Initially, carboxylic acids are reduced *via* proton-coupled electron transfer to get a ketyl radical intermediate, which further gets converted into the ester.

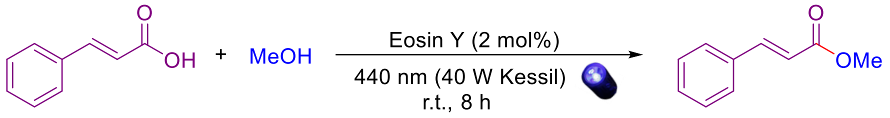


Scheme 1: Strategies for the synthesis of carboxylic esters: a) prior art for the synthesis of α-keto esters; b) prior art for the synthesis of cinnamic esters; c) present work: photoacid catalyzed synthesis of carboxylic esters *via* ketyl radical intermediate.

Results and Discussion

Initially, we set out to investigate the possibility of the esterification reaction assuming that a photoacid cum photoredox catalyst might be useful in generating the PCET complex with the substrate, and Eosin Y fitted the bill very well. Accordingly, the reaction of commercially available cinnamic acid 1a with methanol 2a in the presence of 2 mol% Eosin Y under the irradiation of 440 nm kessil light at room temperature was performed to generate 3a. The reaction resulted in 84% yield of 3a (Table 1, entry 1). A variety of organic dyes as photocatalysts (2 mol%) were tested for this transformation under 440 nm kessil light (Table 1, entries 2-5). While Rhodamine 6G and Rhodamine B produced a very low yield of the product (Table 1, entries 2-3), Rose Bengal and Eosin B failed to produce any 3a (Table 1, entries 4-5). Later, the amount of Eosin Y was optimized (Table 1, entries 6-8) and it appeared that 2 mol% of Eosin Y was most suitable for the formation of the desired product 3a. Further, screening of different wavelengths of light revealed that 440 nm wavelength of light was the optimal wavelength for this reaction (Table 1, entries 9 -11). Control experiments demonstrated the necessity of the photocatalyst and visible-light irradiation, as no detectable product formation was observed in its absence (Table 1, entries 12-13). Quenching of product 3a was observed when the base such as K_2CO_3 was employed in the standard reaction conditions (Table 1, entry 14), indicating the involvement of the photoacid.

Table 1. Summary of the effects of reaction parameters on the reaction efficiency[a]



1a **2a** **3a**

Variation from the above reaction conditions

Entry	Variation from standard conditions	% Yield[b]	Entry	Variation from standard conditions	% Yield[b]
1.	None	**84**	8.	5 mol% of Eosin Y	86
2.	Rhodamine 6G instead of Eosin Y	37	9.	456 nm Kessil	61
3.	Rhodamine B instead of Eosin Y	30	10.	427 nm Kessil	50
4.	Rose Bengal instead of Eosin Y	n.d.	11.	395 nm Kessil	n.d.
5.	Eosin B instead of Eosin Y	n.d.	12.	No catalyst	n.d.
6.	1 mol% of Eosin Y	70	13.	No light	n.d.
7.	3 mol% of Eosin Y	85	14.	1 equiv. of base	n.d.

[a] Reaction conditions: Cinnamic acid (0.5 mmol), Eosin Y (2 mol%), methanol (1 ml), 440 nm Kessil, r.t., 8 h. [b] Isolated yields. n.d. = not detected.

Having optimized the reaction conditions, the scope of the reaction was then investigated. We were pleased to find that the visible-light-mediated esterification reaction was compatible with a diverse range of functional groups (Figure 2). Initially, the esterification reaction of varied cinnamic acids was executed with methanol. Pleasingly, strong electron-donating groups such as hydroxy and moderate electron-donating substituents such as methyl, both at the para position, showed very good yields of the products 3c and 3b in 89% and 86% respectively. Additionally, the dihydroxy-substituted cinnamic acid was also compatible and delivered the desired product 3o in 87% yield. It is worth noting that no prior protection of these hydroxyl functionalities was required under the given conditions. Cinnamic acids with moderate electron-donating substituents as methyl at the ortho, and meta positions furnished the corresponding esters 3l, and 3j in 87% and 85% yields respectively. Strong electron-withdrawing group CF_3 at the para position provided the desired ester 3f with a yield of 71%. Unfortunately, the reaction was not compatible with the nitro group at the para position of the aryl ring to provide the product 3g. Overall, the yield of cinnamic esters having electron donating groups was markedly better than the cinnamic esters embodying electron-withdrawing groups. Assuming that electron-donating groups on cinnamic acids enhanced the nucleophilic character of the oxygen atom of the carboxylic acid that eases proton coupling with the Eosin Y, the above observation came as no surprise. Furthermore, cinnamic acids with halide substituents at ortho, meta, and para positions were subjected to this procedure giving the corresponding esters in good yields (3k, 3h, 3d, 3e, and 3n). Finally, vinyl carboxylic acid carrying naphthalene on one hand and a heterocycle as thiophene on the other transformed successfully into the esters **3p**, and **3q** in 85% and 60% yields respectively. The scope of the photoacid-catalyzed esterification of cinnamic acids leading to cinnamates was further expanded to a range of alcohols. Cinnamic acid **1a** was reacted with several straight-chain alcohols at standard reaction conditions to form the corresponding esters (**3r**-**3t**) in 80-75% yields. Furthermore, primary alcohols containing the cyclic ring and challenging functionalities such as a terminal alkyne group were well tolerated to furnish the corresponding cinnamic esters **3u,** and **3w** in 77% and 75% yields. In addition, benzyl alcohol also worked well in this transformation to form **3v** in 76% yield. Unfortunately, aliphatic acyclic secondary alcohols were unreactive under these conditions. It is apparent that the β- cleavage of alcohols may have adversely affected the reactions in this case (Scheme S3, see SI). Tertiary alcohol such as *t*-BuOH also did not take part in the present transformation. However, cyclic secondary alcohols provided the desired products **3x** and **3y** in 72% and 70% yields respectively. In addition, biologically relevant cholesterol was also tolerated in this esterification of cinnamic acid providing the respective product **3z** in moderate

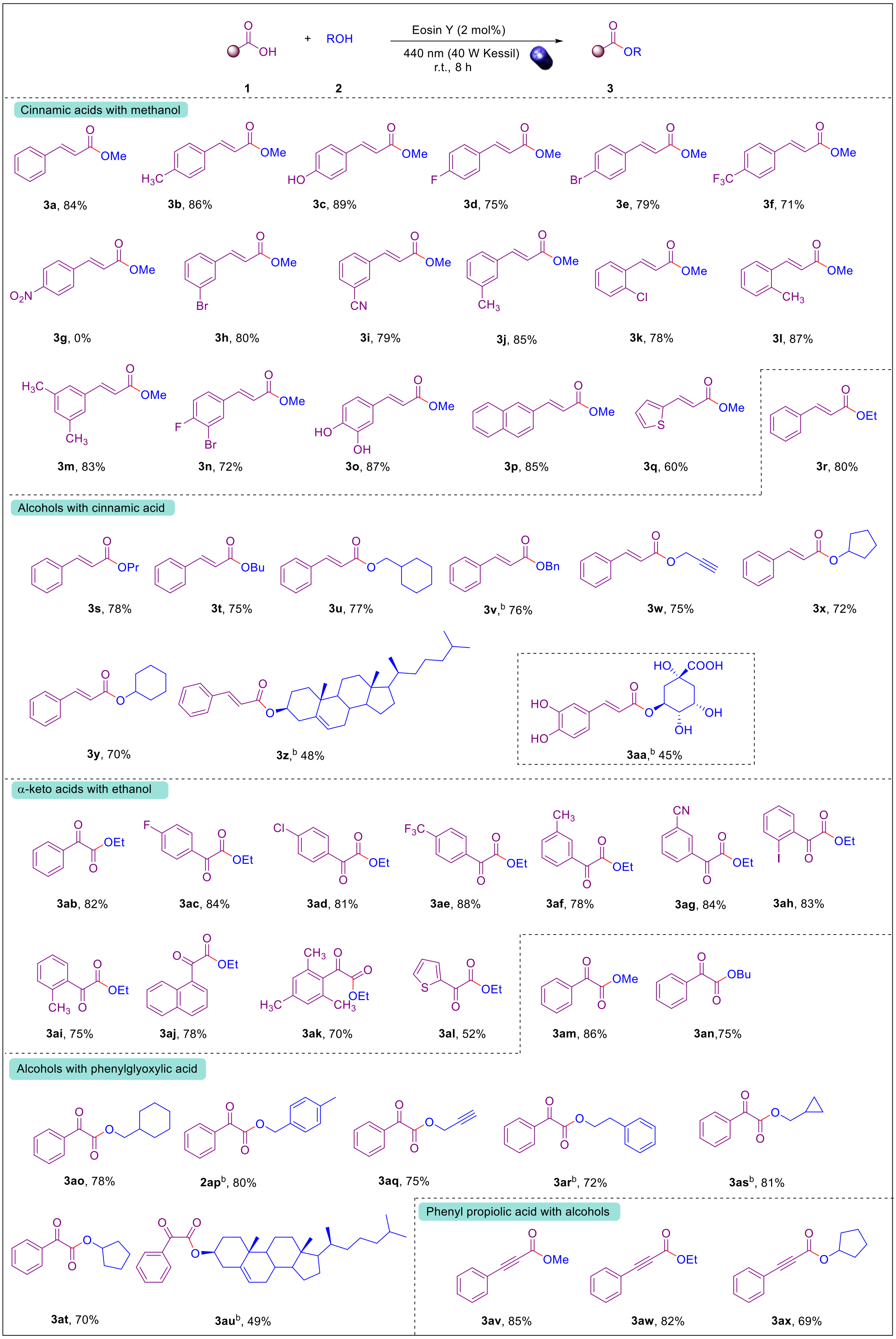


Figure 2: Substrate scope for esterification reaction[a] [a] Reaction conditions: **1** (0.5 mmol), Eosin Y (2 mol%), and alkyl alcohol **2** (1 ml) were kept under photoirradiation using a blue LED (440 nm, 40 W) for 8 h; yields refer to isolated products. [b] alkyl alcohol (1.5 mmol), CH_3CN (1 ml) as a solvent.

yield. Moreover, an anti-inflammatory drug chlorogenic acid **3aa** was synthesized through the coupling of caffeic acid with quinic acid. To further illustrate the synthetic potential of our protocol, we conducted a gram-scale reaction to synthesize methyl cinnamate **3a** (Figure 4A). We successfully performed the model reaction at 1 gram scale, and 0.7303 g of product **3a** was obtained in mildly decreased yield (67% in 12 h).

Having studied the scope of cinnamic acids, we decided to extend our method to the esterification of *α*-keto acids. An additional challenge with *α*-keto acids was the presence of the keto group which might interfere with the formation of the ketyl radical according to our hypothesis. Based on the previous literature,[23] we speculated that after PCET, one electron can be delocalized on both carbon atoms and oxygen of the carbonyl group (Figure 3).

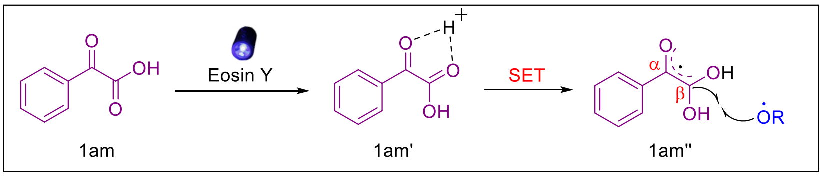
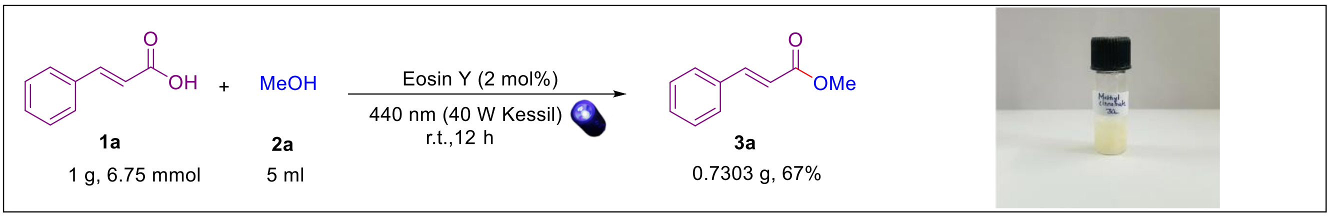


Figure 3: Delocalization of electrons.

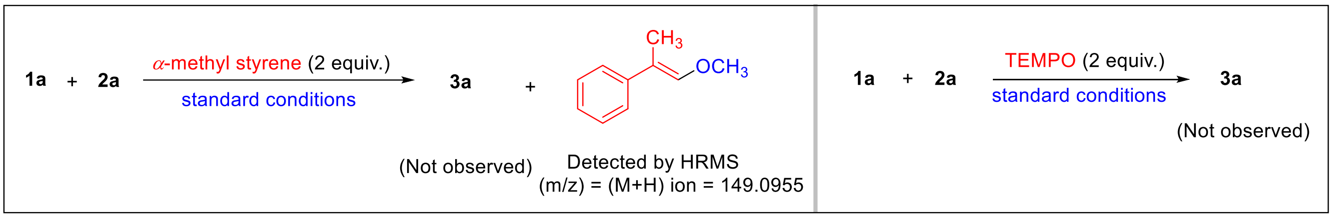
Assuming that electrophilic alkoxy radical might interact with the more nucleophilic carbon radical i.e. *β*-carbon radical of the intermediate **1am"**, the carbonyl function may then not interfere in the esterification reaction. Accordingly, when *α*-keto acids were subjected to similar reaction conditions, desired *α*-keto esters were isolated in 49% to 88% yields (Figure 2). The electron-with-drawing groups such as trifluoromethyl or cyano at para and metapositions, furnished the corresponding products **3ae** and **3ag** in 88% and 84% yields respectively. However, the electron-donating methyl group at the ortho or meta-position of the phenyl ring afforded the *α*-keto esters, **3ai**, and **3af** in 75% and 78% yields respectively. Furthermore, 2,4,6-tri-methyl substituted *α*-keto ester **3ak** was obtained in 70% yield. In contrast to cinnamic acids, the *α*-keto acids bearing electron-withdrawing groups produced *α*-keto esters in higher yield, as compared to those containing electron-donating groups. Considering that the electron-donating group might increase the nucleophilic character of the *α*-keto group instead of the carboxylic acid group of *α*-keto acid resulting in the lower yield of the corresponding ester. In the case of halogen-substituted substrates, the 4-halo substituted derivatives (F and Cl) produced respective products **3ac** and **3ad** in 84% and 81% yields. Likewise, iodo-substituent on phenyl ring at ortho position afforded the product **3ah** in a good yield of 83%. Next, *α*-keto-acids containing polycyclic aromatic rings **3aj** or heteroatom rings **3al** were also found to be compatible with this reaction. Further, the scope of alcohols for photocatalytic esterification of *α*-keto acids was examined (Figure 2). Delightfully, like in the previous series, primary aliphatic alcohols underwent the esterification process smoothly to afford the desired products (**3 am**-**3as**) in good to moderate yields of 86-72%. In addition, the reaction was also successfully applied to cyclic secondary alcohol to furnish **3at** in 70% yield. Also, cholesterol proved to be compatible with the standard reaction conditions, generating the desired compound **3au** in 49% yield. Lastly, we tested our synthetic method on benzoic acid. Unfortunately, no desired product was formed presumably due to its higher reduction potential.[24] However, to our delight, when 3-phenyl propiolic acids were employed as substrates, the reaction went exceedingly well and we achieved the esterification products **3av**, **3aw**, and **3ax** in 85%, 82%, and 69% yields respectively.

Following the identification of a wide range of substrate scope, we shifted our focus towards the detailed exploration of the reaction mechanism. Therefore, several experiments were performed to gain insights into the mechanistic pathway. Initially, the radical nature of this reaction was confirmed by conducting a radical trapping experiment using, *α*-methyl styrene, finding that the esterification product was completely suppressed. Instead, the adduct between methanol and *α*-methyl styrene was observed which was detected by HRMS analysis (Figure S2, See SI). This finding indicated that alkoxy radical was formed during the catalytic cycle. Additionally, employing TEMPO in the reaction mixture completely quenched the product formation (Figure 4B). Electron paramagnetic resonance spectral studies also confirmed the presence of a radical in the reaction. The calculated g value at 2.003 indicated that a carbon radical was being formed during the catalytic cycle (Figure 4C). Furthermore, we observed that there was no overlap between the absorption spectrum of **1a** and the emission spectrum of Eosin Y (Figure 4D). This study proved the absence of energy transfer between cinnamic acid and Eosin Y.[25] Subsequently, transient absorption studies were performed to examine the excited-state dynamics of Eosin Y, with and without **1a**. The transient absorption spectra in the absence of **1a** contained an absorption band in the range of 500 to 550 nm.[26] In contrast, when **1a** was added to Eosin Y, the intensity of the absorption band was altered. These results suggested that the population of electrons in the excited state was perturbed due to the non-covalent interaction between Eosin Y and **1a** (Figure 4E). Further, fluorescence lifetime experiments revealed that cinnamic acid **1a** effectively quenched the lifetime of the photocatalyst Eosin Y (Figure 4F). This dynamic quenching[27] indicated the occurrence of a single electron transfer between **1a** and Eosin Y. The linear Benesi-Hildebrand plot[28] justified the non-bonding interaction between Eosin Y and **1a** (Figure 5A). To clarify the photoacidic nature of Eosin Y, the fluorescence emission spectra were recorded. Eosin Y reacted with **1a** and was converted into its conjugate base that is more active in light, as a result, there was an increase in fluorescence intensity on the consecutive addition of **1a** (Figure 5B).[29] Next, cyclic voltammetry was used to analyze the reduction potential of the substrates (Figure 5C, 5D). The cinnamic acid and phenyl glyoxylic acids displayed a reduction potential value greater than the excited state Eosin Y[9a] that supported the hypothesis of proton coupling before electron transfer. A determined quantum yield of 0.963 was consistent with the absence of a radical chain process (For full details, see supporting information).

(A) Gram scale experiment



(B) Radical trapping experiment



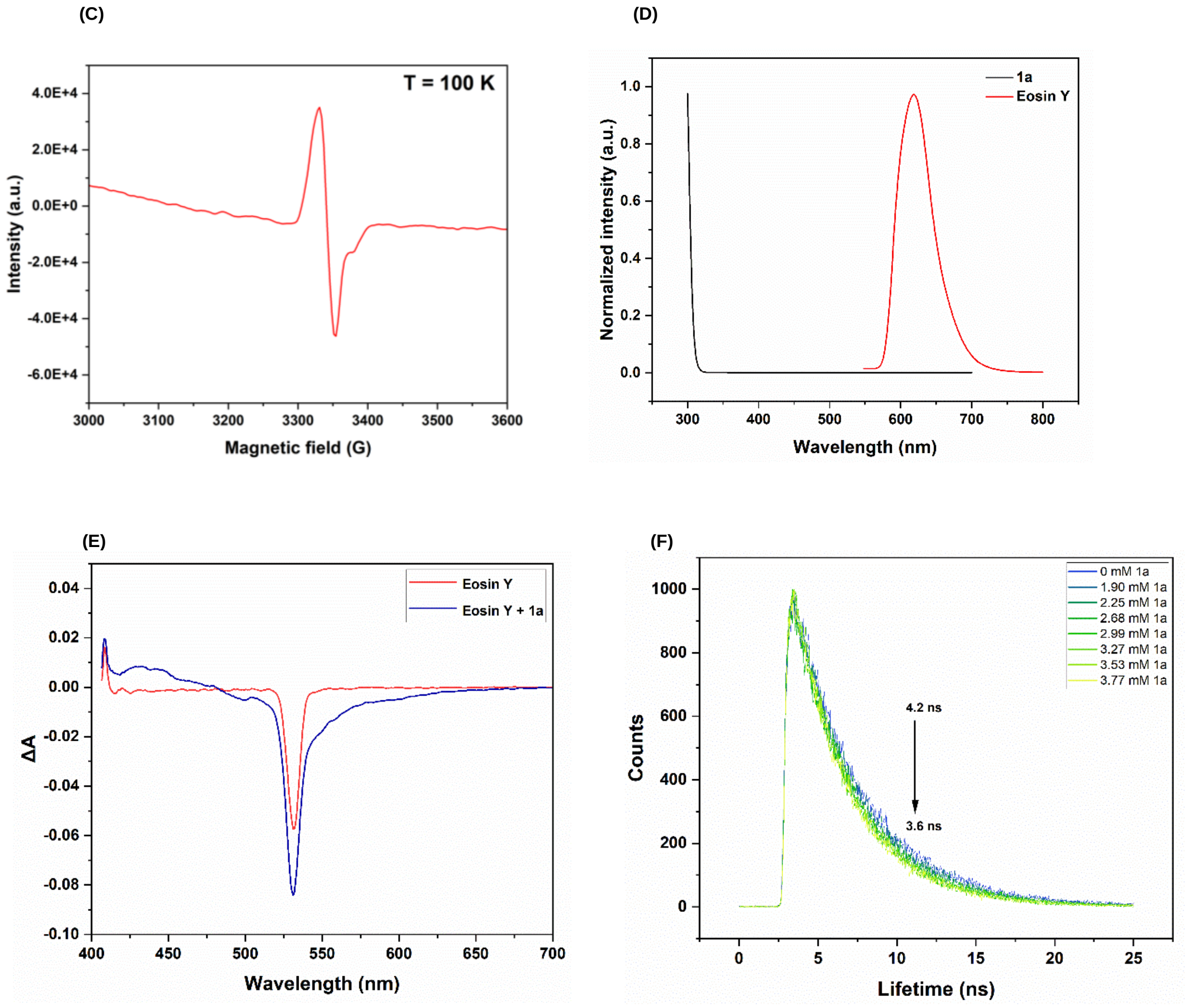


Figure 4: **(A)** Gram scale synthesis of methyl cinnamate; **(B)** Radical trapping experiment. **(C)** EPR spectrum for carbon-centered radical; **(D)** Ground state absorption of Eosin Y and cinnamic acid **1a**. **(E)** Excited state absorption of Eosin Y and Eosin Y with cinnamic acid **1a**; **(F)** Fluorescence lifetime studies of Eosin Y on consecutive addition of cinnamic acid **1a**;

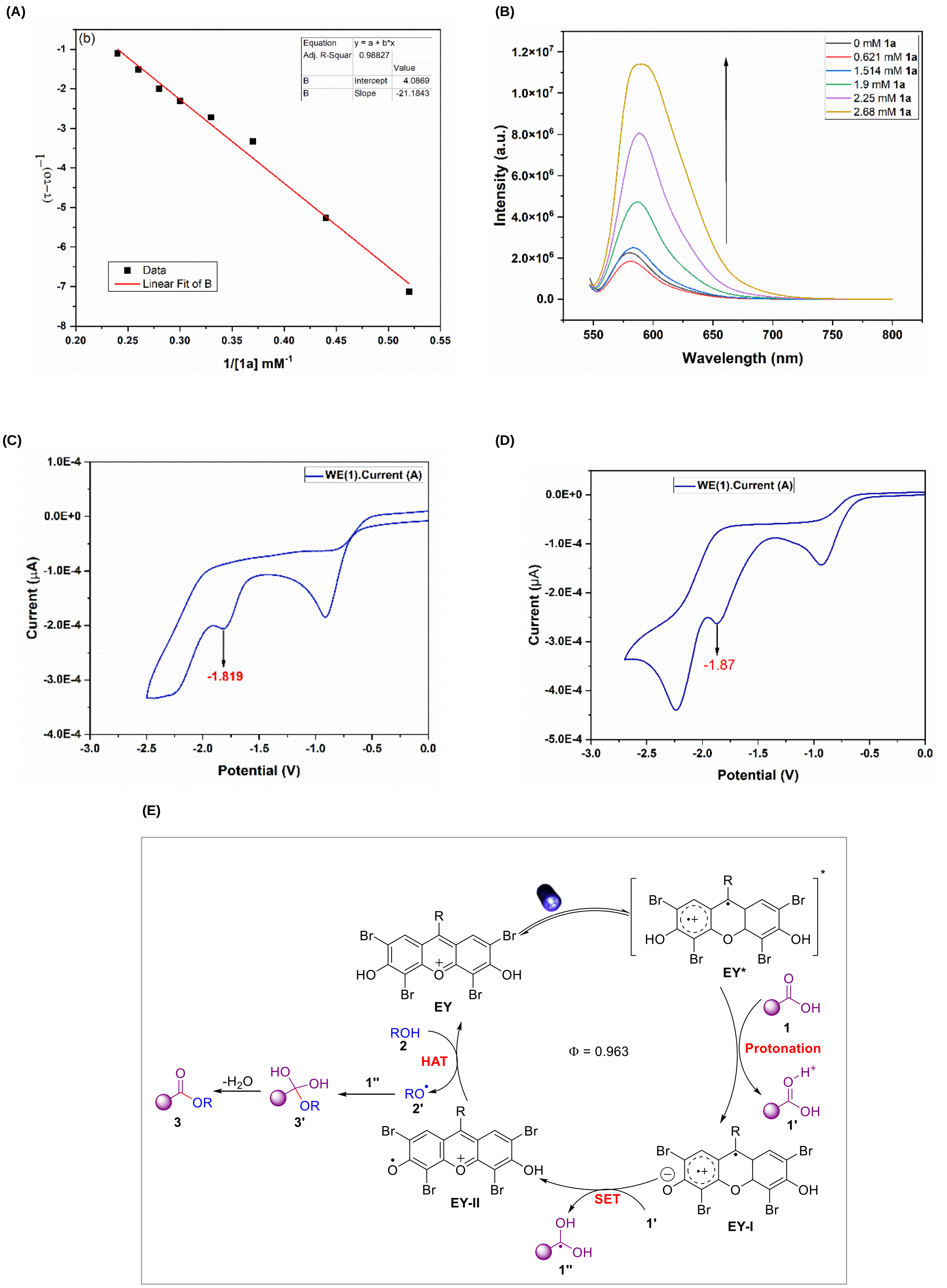


Figure 5: **(A)** Benesi Hildebrand plot depicting 1:1 stoichiometric interaction of Eosin Y with cinnamic acid **1a**; **(B)** Fluorescence emission spectra of Eosin Y with consecutive addition of cinnamic acid **1a**; **(C)** Cyclic voltammetry of cinnamic acid **1a**; **(D)** Cyclic voltammetry of phenyl glyoxylic acid **1am**. **(E)** Proposed mechanism.

According to our experimental results, control experiments, and the previous literature,[15] we developed a working mechanistic hypothesis depicted in Figure 5E. Initially, a more acidic form of Eosin Y was produced in the presence of blue light that could interact with substrate **1**. This interaction allowed a single electron transfer between the substrate cinnamic acid ($E_{½}^{red}$ = -1.82 V vs SCE in CH_3CN) or phenyl glyoxylic acid ($E_{½}^{red}$ = -1.87 V vs SCE in CH_3CN) (Figure 5C and 5D) and Eosin Y ($E_{½}^{ox}$ ($EY^{*}/EY^{+\bullet}$ = -1.15 V vs SCE)][1a] despite their mismatched redox potentials. The single electron transfer induced the formation of the ketyl radical **1"** along with the intermediate EY-II. Subsequently, hydrogen atom transfer from alkyl alcohol **2** to intermediate EY-II furnished alkoxy radical **2'** with the regeneration of Eosin Y. The resulting alkoxy radical reacts with intermediate **1"** to produce a tetrahedral intermediate **3'**. The final product **3** was obtained by the dehydration of the intermediate **3'**.

Conclusion

In conclusion, we have developed photoacid-catalyzed esterification of cinnamic acids, *α*-keto acids, and phenyl propiolic acids. This simple method provides a green approach for the synthesis of esters from aromatic carboxylic acids and alkyl alcohols at room temperature, without any traditional acid catalyst. The method features an operationally simple, high selective, low catalyst loading, and broad substrate scope. In addition, mechanistic studies support the proton-coupled electron transfer pathway and the generation of the ketyl radical employing Eosin Y as a photoacid catalyst. Our laboratory is currently engaged in further research utilizing photoacids for synthetic transformations.

Associated Content

The data that support the findings of this study are available in the supplementary material of this article.

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Notes

The authors declare no competing financial interest

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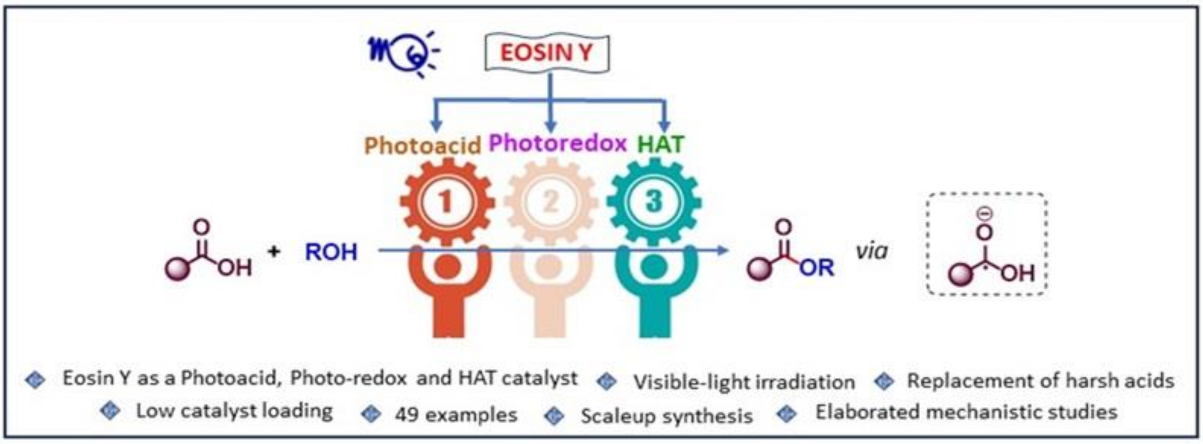
Table of Content

Esterification of Carboxylic Acids utilizing Eosin Y as a Photoacid Catalyst



Photoacid-catalyzed esterification of carboxylic acids with alkyl alcohols is presented. Herein, Eosin Y acted as a photoacid, photoredox, and hydrogen atom transfer agent in the presence of blue light. Mechanistic studies suggested that this transformation proceeded *via* ketyl radical derived from the carboxylic acids.