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ARTICLE

Ambient and aerobic carbon-carbon bond cleavage toward α-ketoester synthesis by transition-metal-free photocatalysis

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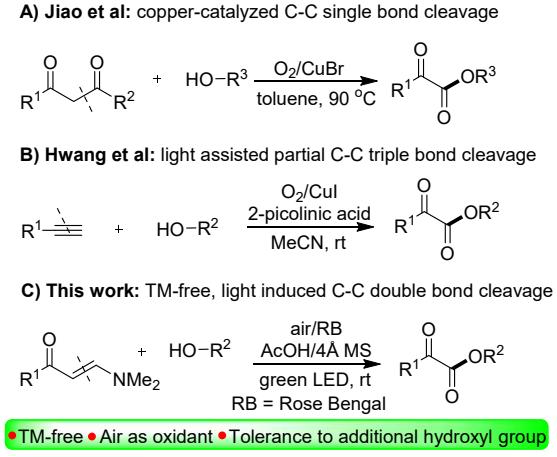
The α-oxoesterification of the C=C double in readily available enaminones enabling efficient synthesis of α-ketoesters is developed. The reactions showing general tolerance to the reactions of primary and secondary alcohols proceed well under air atmosphere via Rose Bengal (RB)-based photocatalysis. Particularly, this mild synthetic method has been discovered to tolerate various polyhydroxylated substrates such as phenolic alcohol, diol and triol with excellent selectivity of mono-oxoesterification. More noteworthy, the α-ketoester functionalized 16-dehydropregnenolone acetate resulting from the elaboration on natural product has been obtained practically.

Introduction

Scissoring C-C bond constitutes one of the central tasks of modern organic synthesis because of its exceptionally highly application potential associated with the ubiquitously available and stable C-C bonds in nature.[1] Particularly, the C=C double bond cleavage is a mode of most widespread utilization for the balanced stability and reactivity of such bonds, which can take place in the forms of both partial[2] and full bond cleavage.[3] As typical alkene derivatives, enaminones have in recently years been disclosed with amazingly versatile utilities in diversity oriented synthesis.[4] Notably, although the C=C double bond cleavage of enaminones has been observed early in 1970s,[5] it is in the recent couple of years that many valuable synthetic applications have been disclosed with the cleavage of such double bonds. For example, the partial cleavage of enaminone C=C double have been successfully employed in the synthesis of benzothiazole functionalized vicinal diketone structure,[6] the acyl migration-based synthesis of 1,5-disubstituted 1,2,3-triazoles,[7] and the β,β-diaryl propiophenones.[8] On the other hand, the full cleavage of enaminone C=C double bond has been successfully employed in designing new synthetic routes to α-keto amides and thioamides,[9] pyridines,[10] vicinal diketones,[11] quinolines,[12] β-carbamoylenamines,[13] and β-ketophosphonates.[14] With the success of these results, disclosing more sophisticated synthetic application of such C-C bond cleavage process is highly expectable.

α-Ketoesters are valuable chemicals displaying broad application as synthetic building blocks and biologically relevant candidates.[15] Currently, the α-ketoesters can be synthesized by several different approaches. Typically, the direct esterification of α-keto acids/halides,[16] oxidation of α-hydroxyl, halogenated esters or aryl acetimidates,[17] Pd-catalyzed double carbonylation of aryl halides,[18] Cu-catalyzed C-H esterification of α-ketoaldehydes,[19] Rh-catalyzed coupling of aryl boronic acids and cyanoesters,[20] and tandem C-H oxygenation/esterification of methyl ketones.[21] Because substrates with high level functionalization, transition metal catalysis and/or harsh oxidation conditions are usually required in the known methods, it is yet highly demanding to develop methods for the α-ketoesters synthesis by using easily available substrates, without relying on transition metal catalyst or strong oxidant.

In 2013, Jiao and co-workers reported their pioneering work in α-ketoester synthesis by copper-catalyzed reactions of 1,3-diketones and alcohols via the cleavage of a sigmatic C-C bond (Scheme 1A).[22] Rather recently, Hwung et al developed an alternative approach of copper-catalyzed reactions between terminal alkynes and alcohols with the assistance visible irradiation, wherein the π-bonds in the alkynes have been cleaved (Scheme 1B).[23] Alongside the known modes of



Scheme 1 Scissoring carbon-carbon bonds for α-ketoester synthesis

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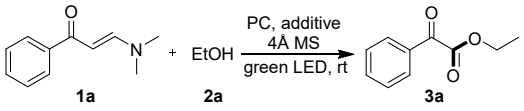
scissoring C-C single and C≡C triple bonds, we report herein the first method for α-ketoester synthesis by scissoring C=C double bond with sustainable photocatalysis (Scheme 1C).[24] As complementary option to known methods, this work has been identified with several particular advantages: a) free of transition metal reagent; b) aerobic rather than pure O_2 oxidation; c) excellent chemo-selectivity of single alcoholic OH transformation with diol, triol and phenolic alcohol substrates.

Results and discussion

At the outset, the enaminone **1a** and ethanol **2a** were employed in the presence of photocatalyst (PC) with green LEDs irradiation. First, the reaction in the presence of RB and molecular sieves (MS) in DMF gave the α-ketoester **3a** with 39% yield (entry 1, Table 1). With the inspiration, this reaction was then further performed in different medium, including toluene, THF, water, dioxane and EtOH. The experiments implied that EtOH was the most proper medium for this reaction (entries 2-6, Table 1). Later, the experiments with different PCs such as Eosin B, disodium Eosin Y, and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ were executed, wherein RB turned out to be the most practical PC by providing **3a** with considerably higher yield (entries 7-9, Table 1). The control entry in the absence of either PC or light irradiation did not give the target product (entries 10-11, Table 1). The reaction under nitrogen gas did not provide **3a**, either (entry 12, Table 1). Delightfully, employing 2 equiv AcOH as an additive led to significant improvement on the reaction (entry 13, Table 1), which might be attributed to the possible activation effect of the acid to the ring opening of 1,2-dioxetane intermediate (See Scheme 3). Benzoic acid was also able to enhance the product yield, but with inferior effect (entry 14, Table 1). However, varying the loading of AcOH did not lead to better results (entries 15-16, Table 1). Complementarily, a parallel experiment without 4Å MS led to drastic drop of **3a** yield (entry 17, Table 1). Finally, reducing the volume of EtOH to 1 mL could afford **3a** with even higher yield (entry 18, Table 1).

To illustrate the synthetic scope, this photocatalytic α-oxoesterification reaction of enaminones was first executed by employing various enaminones **1** to react with ethanol **2a**. As given in Table 2, the synthesis displayed general tolerance to enaminones functionalized with aryl backbone. The enaminones with electron donating group in the phenyl ring reacted with EtOH to give α-ketoesters with higher yields than equivalent reactions using enaminones containing electron withdrawing group functionalized phenyls (**3a**-**3c** *vs* **3d**-**3g**, Table 2). On the other hand, the site of the substituent in the phenyl ring did not show impact on the product yield (**3h**-**3k**, Table 2). More notably, the enaminones functionalized with double substituted phenyl (**3l**-**3m**, Table 2), fused aryl (**3n**-**3o**, Table 2) and heteroaryl (**3p**-**3q**, Table 2) also smoothly took part in the α-ketoester synthesis with generally good yield. The most convictive example, however, was the synthesis of product **3r** via post elaboration on the natural product 16-

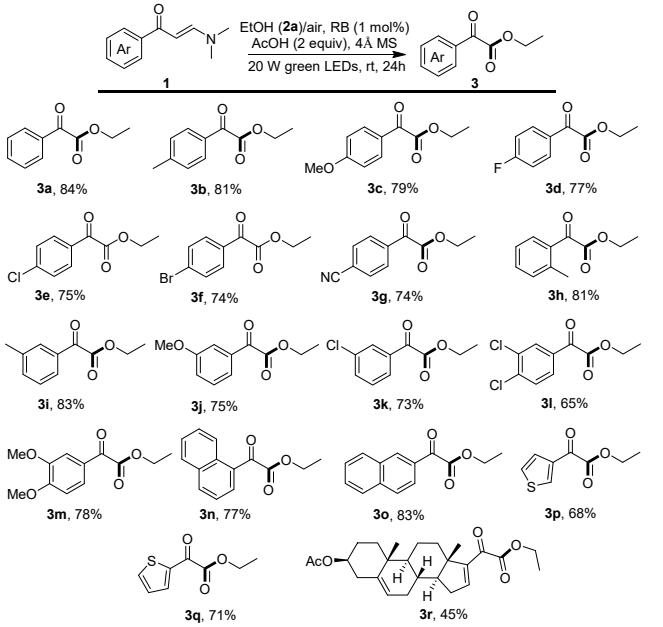
Table 1 Optimization on photocatalysis conditions[a]



entry	PC	solvent	additive	yield (%)[b]
1	RB	DMF	-	39
2	RB	toluene	-	0
3	RB	THF	-	trace
4	RB	H_2O	-	0
5	RB	1,4-dioxane	-	27
6	RB	EtOH	-	48
7	Eosin B	EtOH	-	trace
8	Na_2[Eosin Y]	EtOH	-	40
9	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	EtOH	-	8
10	-	EtOH	-	0
11[c]	RB	EtOH	-	0
12[d]	RB	EtOH	-	0
13	RB	EtOH	AcOH	76
14	RB	EtOH	$PhCO_2H$	67
15[e]	RB	EtOH	AcOH	52
16[f]	RB	EtOH	AcOH	63
17[g]	RB	EtOH	AcOH	49
18[h]	RB	EtOH	AcOH	84

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (4 mmol, or 2 mL when used as solvent), PC (0.002 mmol), solvent (2 mL), 4Å molecular sieve (80 mg) and additive 0.4 mmol. Stirring with the irradiation of 20W green LEDs at room temperature for 24 h. [b]Yield of isolated product based on **1a**. [c]Reaction in black atmosphere. [d]Under nitrogen atmosphere. [e]With 0.2 mmol AcOH. [f]With 0.6 mmol AcOH. [g]Without 4Å molecular sieve. [h]Reaction using 1 mL EtOH.

Table 2 Scope of enaminones for the photocatalytic α-ketoester synthesis[a,b]

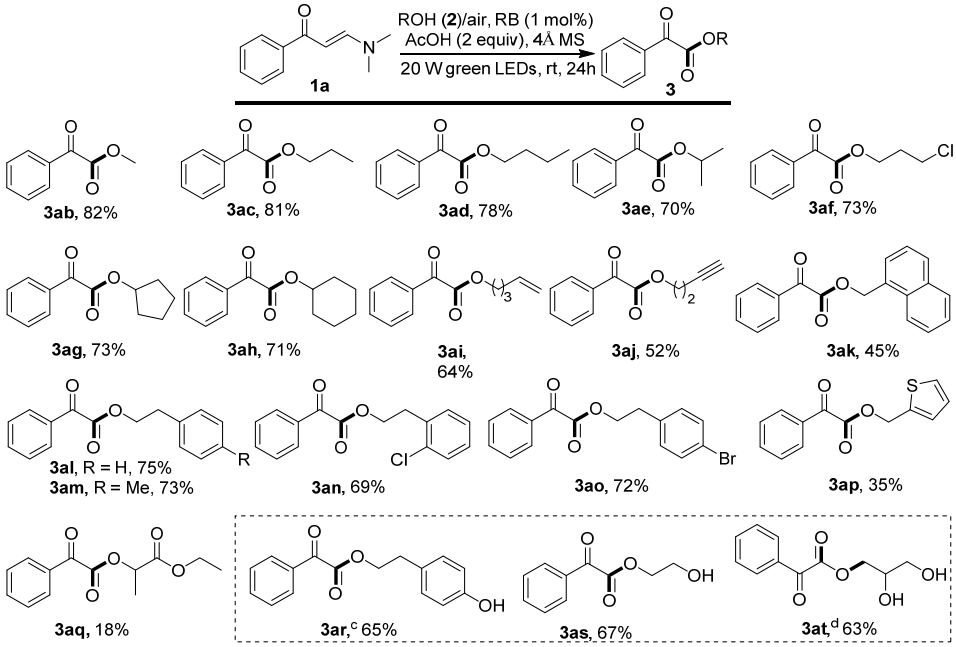


[a]Conditions: **1** (0.2 mmol), **2a** (1 mL) RB (0.002 mmol), AcOH (0.4 mmol) and 4Å MS (80 mg), stirred at rt with the irradiation of 20 W green LEDs under air atmosphere. [b]Isolated yield based on **1**.

dehydropregnenolone acetate. It should be noted that such a natural product derivative had not been previously synthesized in any known literature. In the reaction using (*E*)-4-(dimethylamino)but-3-en-2-one, an alkyl-based enaminone with EtOH, no expected product was observed.

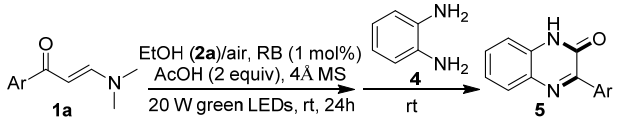
In further efforts, the scope of alcohols for this photocatalytic oxoesterification reaction was examined. Delightfully, the employment of primary and secondary alcohols, including linear and branched alkyl alcohols (**3ab**-**3ae**, Table 3), haloalkyl alcohol (**3af**, Table 3), cyclic alcohols (**3ag**-**3ah**, Table 3), alkenyl and alkynyl functionalized alcohols (**3ai**-**3aj**, Table 3), and aryl/heteroaryl functionalized alcohols (**3ak**-**3ap**, Table 3) all took part in the titled reaction to provide the diverse α-ketoester products. In addition, the highly functionalized alcohol such as ethyl lactate could also be transformed into the corresponding α-ketoester derivative (**3aq**, Table 3). A particularly noteworthy point was that the present reaction tolerated well to the substrates containing additional sensitive hydroxyl group(s) whereby only one alcohol hydroxyl participated the reaction. Thus, the synthesis of phenol functionalized product **3ar** was acquired via the reaction of 4-(2-hydroxyethyl)phenol (Table 3). And the diol (ethane-1,2-diol) and triol (glycerol) incorporated enaminone **1a** to afford hydroxyl functionalized α-ketoester **3as**, **3at** with excellent chemo-selectivity as no product resulting from the reaction involving more than one hydroxyl group was isolated from these entries (Table 3). According to the in hand results, the steric hindrance of alcohol was found to evidently effect the reaction. Tertiary alcohol such as *t*-BuOH did not take part in the present transformation, and those secondary alcohols led to the formation of products with slightly lower yields than equivalent primary alcohols (**3ae**, **3ae**-**3ah** vs **3ab**-**3ac**, Table 3).

Table 3 Scope of alcohols for the photocatalytic α-ketoester synthesis[a,b]



[a]General conditions: **1a** (0.2 mmol), alcohol **2** (1 mL), RB (0.002 mmol), AcOH (0.4 mmol) and 4Å MS (80 mg), stirred at rt with the irradiation of 20 W green LEDs under air atmosphere. [b]Isolated yield based on **1**. [c]With 4-(2-hydroxyethyl)phenol (1 mmol) in DMF (1 mL). [d]With glycerol ((1 mmol) in DMF (1 mL).

In the process of exploring further expanded application of this photocatalytic transformation, we attempted to employ *o*-phenylenediamine **4** to the reaction system, and we were delighted to observe that stirring at rt enabled the practical synthesis of quinoxalin-2(1H)-ones **5** with both satisfactory yields and substrate tolerance (Scheme 2), illustrating the high usefulness of this photocatalytic system in the synthesis of different types of organic molecules.

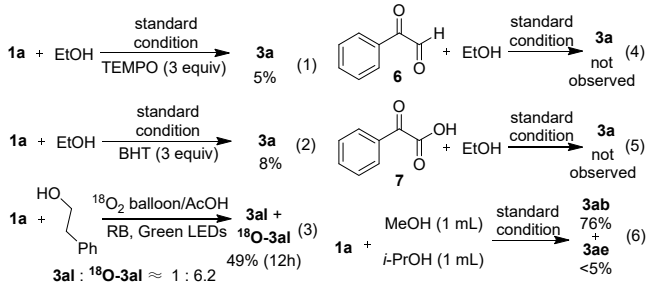


5a, Ar = Ph, 77% **5b**, Ar = 4-MeC_6H_4, 74% **5c**, Ar = 4-MeOC_6H_4, 74%
5d, Ar = 4-FC_6H_4, 69% **5e**, Ar = 4-ClC_6H_4, 63% **5f**, Ar = 4-BrC_6H_4, 67%
5g, Ar = 3-MeC_6H_4, 76% **5h**, Ar = naphth-2-yl, 74% **5i**, Ar = thiophen-2-yl, 66%

Scheme 2 One-pot synthesis of quinoxalin-2(1H)-ones

In order to probe the reaction mechanism, a series of control experiments were then performed. In the control experiments employing free radical scavenger, TEMPO and BHT both exhibited potent inhibition to the reaction (eqs 1 and 2), supporting the free radical production process in the reaction. In addition, the reaction under $^{18}O_2$ gave the ^{18}O-labeled product **^{18}O-3al** as the major product (eq 3), confirming that the air was the oxygen source in the newly formed C=O group. Furthermore, the α-ketoaldehyde **6** and α-ketoester **7** were

employed to react with EtOH under the standard reaction conditions, respectively. Neither gave the product **3** (eqs 4 and 5), suggesting that they were not the possible intermediate in the titled reaction. In a reaction employing simultaneously EtOH and *i*-PrOH with **1a**, the product **3ab** was produced with high yield, while only tiny amount of product **3ae** resulting from the reaction of *i*-PrOH was observed, confirming the negative effect of the alcohol steric hindrance to this oxoesterification reaction (eq 6).



Following these control experiments, we then probed potential route of energy transfer in the photocatalytic reaction. Thus, the effect of enaminone **1a** to the fluorescence intensity of RB catalyst was measured at different concentration. As outlined in Figure 1, the results indicated that the enaminone did not quench the RB catalyst, suggesting that the interaction of RB with the molecular oxygen in the air was the process of transferring the energy.

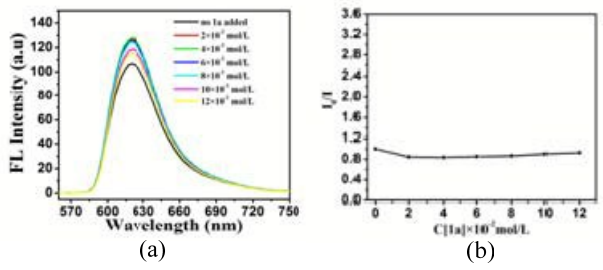
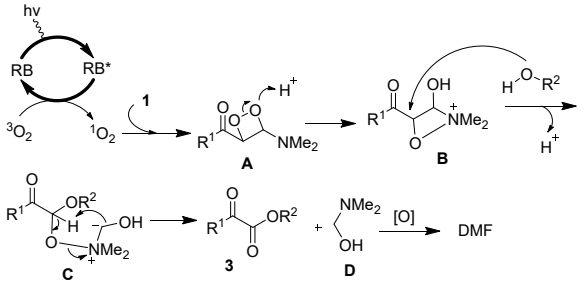


Figure 1 (a) The quenching of RB fluorescence emission with enaminone **1a**; (b) Stern-Volmer plot. I_0 is the inherent fluorescence intensity of RB. I is the fluorescence intensity of RB in the presence of **1a**.

With the in hand results, the mechanism for the reaction is proposed (Scheme 3). Initially, the visible light irradiation to RB gives rise to excited RB* species, which activates molecular oxygen to provide active singlet oxygen $^1O_2$.[25] This active oxygen then couples the C=C double bond of enaminone to



Scheme 3 The proposed reaction mechanism

generate 1,2-dioxetane **A**. The proton acid then promotes the ring opening of **A** and a subsequent N-O bond formation to access intermediate **B**. The nucleophilic attack of alcohol to **B** provides zwitterion intermediate **C** which undergoes decomposition to provide products **3** and amino alcohol **D**. The alcohol **D** may get oxidized to DMF under the present oxidative conditions.

Conclusions

In conclusion, by means of a newly developed photocatalytic method free of any transition-metal reagent, the C=C double of *N,N*-disubstituted enaminones is efficiently tailored as an approach for α-ketoester synthesis. Besides, the one-pot synthesis of quinoxalin-2(1*H*)-ones are practically achieved by making use of this C=C bond cleavage process via one-pot operation. As a transition metal-free, aerobic, broadly applicable and highly chemo-selective protocol, this method affords a useful and sustainable new option for the synthesis of diverse α-ketoesters.

Experimental

General procedure for the synthesis of of α-ketoesters 3. In a 15 mL test tube were charged with enaminone **1** (0.2 mmol), RB (0.002 mmol), AcOH (0.4 mmol), alcohol **2** (1 mL liquid alcohol, or 1 mmol solid alcohol substrate in 1 mL DMF) and 4Å molecular sieve (80 mg). The mixture was irradiation with 20 W green LEDs for 24h at room temperature. Upon completion (TLC), the mixture was moved to the round bottom flask, and the reaction tube was washed additionally with ethyl acetate (5mL) to fully transfer the residue. The solvent in the flask was then removed at reduced pressure, and the residue was purified by silica gel column chromatography with the elution of mixed ethyl acetate and petroleum ether (v/v = 1:20-1:3). For the reaction of solid alcohols, after the reaction completion, water (5 mL) was added to the vessel, and the suspension was extracted with ethyl acetate (3 ×10 mL). The combined organic phase was dried over Na_2SO_4. After filtration, the acquired solution was employed to reduced pressure to remove the organic solvent. And analogous chromatographic purification using mixed ethyl acetate and petroleum (v/v = 1:8) as eluent was executed to the residue obtain corresponding products.

General procedure for the synthesis of quinoxalin-2(1*H*)-ones 5. In a 15 mL test tube were charged with enaminone **1** (0.2 mmol), RB (0.002 mmol), AcOH (0.4 mmol), alcohol **2** (1 mL liquid alcohol, or 1 mmol solid alcohol substrate in 1 mL DMF) and 4Å molecular sieve (80 mg). The mixture was irradiation with 20 W green LEDs for 24h at room temperature. Subsequently, diamine **4** (0.2 mmol) solved in EtOH (1 mL) was added, and the resulting mixture was further stirred at room temperature for 12 h. Upon completion (TLC), the mixture was moved to the round bottom flask, and the reaction tube was washed additionally with ethyl acetate (5mL) to fully transfer the residue. The solvent in the flask was then removed at reduced pressure, and the residue was purified by silica gel column

chromatography with the elution of mixed ethyl acetate and petroleum ether (v/v = 1:5).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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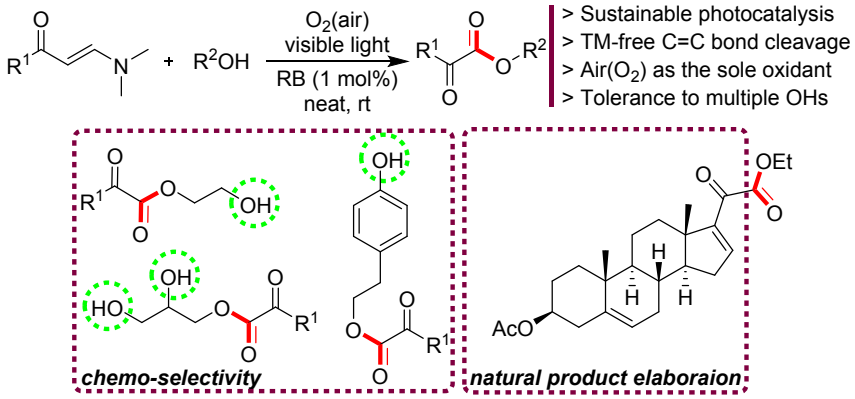
TOC



With low loading of Rose Bengal (1 mol%) and green LEDs irradiation, α-ketoesters are efficiently synthesized with excellent product diversity and selectivity via the ambient cleavage of enaminone C=C double bond.