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Visible light-induced intermolecular radical addition: facile access to γ-ketoesters from alkyl-bromocarboxylates and enamines†

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A highly efficient addition of alkyl α -bromocarboxylates to enamines by visible light-induced photoredox catalysis is reported. Compared with traditional methods, the reaction described here provided an alternative route for the construction of valuable γ -ketoesters in generally good yields.

Traditional photo-initiated radical reaction was considered to be an alternative method in the field of synthetic chemistry. However, the poor selectivity and the need for specialized UV reactors considerably limited its application. Visible light serves as a new energy source of photo-induced radical reactions and photoredox reactions is showing the power of a radical-involving reaction in organic synthesis. It has attracted considerable attention from numerous researchers and has emerged as a growing field because the C-X bond formation continues to be a demand in organic synthesis.¹ Free radicals, which are generated by photoredox catalysis, can react to construct the bond of C-X (X = C, S, N, O). Because C-C bond formation has been documented by the groups of Stephenson,² Gagné,³ Reiser⁴ and Masson,⁵ Xiao et al. have also reported the formation of C-O.⁶ Despite these significant advances, the exploitation of novel and efficient organic radical precursors and the extension of their application to more reactions remains highly attractive.⁷

 γ -Ketoesters are important synthetic intermediates in organic synthesis. The traditional radical synthetic methods are radicals that were irradiated by AIBN or organotin reagents. Hosomi *et al.* have reported the reaction of ethyl 2-bromopropanoate with tributylstannyl enolate to give γ -ketoesters initiated by AIBN in benzene at 80 °C (Scheme 1a).⁸ Kim *et al.* also reported that the photo-stimulated reaction of ethyl α -iodoacetate with vinyl-triflate and hexamethylditin in benzene under irradiation at 300 nm for

(a) $\xrightarrow{\text{Der}}_{0} \xrightarrow{\text{OSnBu}_{3}}_{0}$ $\xrightarrow{\text{AIBN}}_{\text{PhH, 80 °C, 4 h}}$ $\xrightarrow{\text{O}}_{0} \xrightarrow{\text{OEt}}_{0}$ (b) $1 \xrightarrow{\text{OEt}}_{0} \xrightarrow{\text{OSO}_2CF_3}_{0}$ $\xrightarrow{\text{OSO}_2CF_3}_{0}$ $\xrightarrow{\text{OOEt}}_{0}$ $\xrightarrow{\text{OEt}}_{0}$ $\xrightarrow{\text{OOEt}}_{0}$ $\xrightarrow{\text{OOEt}}_{0}$ $\xrightarrow{\text{OOEt}}_{1}$ $\xrightarrow{\text{OOEt$

Scheme 1 Addition of radical to the unsaturated compounds.

5 h afforded the target product (Scheme 1b).⁹ However, it is still quite limited because organotin compounds were used as either starting material or as a radical initiator, which were not environment-friendly in the reaction.

A carbon-centered radical added to an unsaturated carbon atom in an appropriate acceptor, followed by the fragmentation of the adduct radical, is the key chain-extension method for the construction of carbon–carbon bonds. The generation of carbonyl alkyl radicals is well-known from an alkyl α -bromocarboxylate under visible light catalyzed reactions.¹⁰ Lei *et al.* succeeded in the addition of carbonyl alkyl radicals and alkenes to obtain unsaturated ester compounds (Scheme 2, path a). We attempted to find an appropriate acceptor to trap the carboncentered electron-deficient radical, followed by the transformation of one electron, to form an iminium cation, and eventually, γ -ketoesters were achieved (Scheme 2, path b). Considering that the α -carbonyl alkyl radical is relatively electrophilic, electronrich alkenes may be beneficial to the reaction.¹¹ Therefore, enamines were preferentially chosen to test the reaction.

We initiated our investigation by examining the reaction of *N*-(1-styryl)morpholine and ethyl 2-bromopropanoate with Ru(bpy)₃Cl₂ (2 mol%) by employing Et₃N (40 mol%) in DMF under a 23 W household fluorescent lamp irradiation (Table 1, entry 1). Fortunately, the reaction occurred in 16% yield. When NaHCO₃ (1 eq.) was added, the reaction gave a slightly higher yield (Table 1, entry 2). Na₂CO₃ was also examined, and a slightly better result was obtained (Table 1, entry 3). When we changed the base to K_2CO_3 , a higher yield was achieved

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Scheme 2 Addition of radical to the unsaturated compounds under visible-light catalyzed reaction.

Table 1 Optimization of the reaction conditions

Ĺ	1a	Br OEt O 2a	Ru(bpy) ₃ Cl ₂ , base Et ₃ N, additive Visible light	OEt O
Entry	Base	Solvent	Additive	Yield ^b (%)
1		DMF		16
2	NaHCO ₃	DMF		31
3	Na_2CO_3	DMF		55
4	K_2CO_3	DMF		64
5	K_3PO_4	DMF		12
6	^t BuOK	DMF		4
7 ^c	Et_3N	DMF		11
8	K_2CO_3	CH_3CN		40
9	K_2CO_3	DMA		37
10	K_2CO_3	DCM		8
11	K_2CO_3	Toluene		5
12	K_2CO_3	NMP		35
13	K_2CO_3	DMSO		16
14	K_2CO_3	DMF	Pyridine	74
15	K_2CO_3	DMF	4-Methoxypyridine	90 (86^d)
16^e	K_2CO_3	DMF	4-Methoxypyridine	87
17 ^{<i>f</i>}	K_2CO_3	DMF	4-Methoxypyridine	89
18	K_2CO_3	DMF	DMAP	33
19 ^g	K_2CO_3	DMF	4-Methoxypyridine	0
20^{h}	K_2CO_3	DMF	4-Methoxypyridine	10
21^i	K_2CO_3	DMF	4-Methoxypyridine	47
22 ^j	K_2CO_3	DMF	4-Methoxypyridine	35

^{*a*} Conditions: **1a** (0.5 mmol), **2a** (1 mmol), Ru(bpy)₃Cl₂ (0.01 mmol), Et₃N (0.2 mmol), 4-methoxypyridine (0.2 mmol), base (0.5 mmol), solvent (2 mL), irradiation with a 23 W household light bulb at about 35 °C for 24 h. ^{*b*} GC yields based on dibenzyl ether as an internal standard. ^{*c*} Et₃N (0.75 mmol). ^{*d*} Isolated yield. ^{*e*} 4-Methoxypyridine (0.1 mmol) was used. ^{*f*} 4-Methoxypyridine (0.4 mmol). ^{*g*} Without light. ^{*h*} Without catalyst. ^{*i*} **1a** (1 mmol), **2a** (0.5 mmol), GC yield based on dibenzyl ether as an internal standard. ^{*J*} O₂ balloon.

(Table 1, entry 4). However, a poor result was obtained when K_3PO_4 or ^{*t*}BuOK was added to the reaction (Table 1, entries 5 and 6). We know that Et_3N not only acted as a reductant but also as a base in the reactions; however, when Et_3N (1.5 eq.) was used as the base, an even worse result was obtained (Table 1, entry 7). We then screened

the solvents in the presence of K_2CO_3 as the base for the reaction. Among the tested solvents, DMF was proven to be the best for this transformation (Table 1, entries 8-13). The reaction proceeded with the formation of acetophenone as a by-product during the reactions. Thus, we tried to add some pyridine derivatives (Table 1, entries 14-19), which were claimed to be beneficial for improving reactivity in similar reactions.^{1m,10} When we applied pyridine to the reaction, the yield was slightly improved (Table 1, entry 14). When 40 mol% of 4-methoxypyridine relative to enamine was added to the reaction, an 86% isolated yield was obtained with significantly less by-product (Table 1, entry 15). There is no obvious influence with slightly less or more 4-methoxypyridine in the reaction (Table 1, entries 16 and 17). Other pyridine derivatives, such as DMAP, did not give a satisfactory yield (Table 1, entry 18). Control experiments showed that both Ru(bpy)₃Cl₂ and visible light are essential for this reaction. When the reactions were conducted without a catalyst or in dark, essentially no products were formed regardless of the background reaction (Table 1, entries 19 and 20). When the molar ratio of 1a and 2a was exchanged from 1:2 to 2:1, only a 47% yield was obtained (Table 1, entry 21). Moreover, we also conducted the reaction with an O₂ balloon, and only a 35% yield was obtained, which indicated that a cage effect existed in the reaction (Table 1, entry 22).¹² In the following experiments, different enamines (1a-1d) of acetophenone were prepared¹³ to test their reaction with 2a (Scheme 3). When 1b was employed as the substrate, the best result (94% yield) was obtained. Other enamines, such as 1c and 1d, also provided good results.

Next, we evaluated the substrate scope of this reaction with enamines prepared from piperidine and different ketones, and the results are listed in Table 2.

Enamines **1b**, **1e–1l** derived from aryl methyl ketone provided good yields of keto esters. A significant electronic effect was observed in the reactions of **1h** and **1i**. The presence of an electron-withdrawing group decreased the reactivity of the enamine, whereas an electron-donating group increased the reactivity of enamine. As a result, the reaction of **1h** gave **3h** in moderate yield compared with the reaction of **1i**, which gave **3i** in excellent yield. It appears that steric hindrance did not have a remarkable effect on the reaction when **1j** was used as the substrate; **3j** was obtained in 97% yield. Enamine **1k** (*E*) prepared from propiophenone can react smoothly to give the desired product in 66% yield. Moreover, the reaction of enamine of tetralone **1l** was also conducted, which gave the desired product in poor yields (**3l**, 33% yield).

In addition, we extended this radical addition reaction to other α -carbonyl alkyl or benzyl bromides, and similar results



Scheme 3 Reactions of different enamines (1a-1d) with 2a.

Table 2 Reactions of enamines with 2a^a

	$N_{R}^{R^{1}+}$	Br OEt	$\frac{\text{Ru(bpy)}_{3}\text{Cl}_{2}}{\text{visible light}} \xrightarrow[R^{1}]{0} R^{1}$,OEt
	1b,1e-1l	2a	3b, 3e-3l	
Entry	R		\mathbb{R}^{1}	$\operatorname{Yield}^{b}(\%)$
1	$C_{6}H_{5}$ (1b)		Н	94
2	$4 - Me - C_6 H_4$ (1e)		Н	92
3	$4 - F - C_6 H_4 (\mathbf{1f})$		Н	92
4	$4 - Cl - C_6 H_4$ (1g)		Н	91
5	$4-CF_{3}-C_{6}H_{4}$ (1h)		Н	78
6	$4 - MeO - C_6 H_4$ (1i)		Н	96
7	2-Me-C ₆ H ₄ (1j)		Н	97
8	C_6H_5 (1k)		Me	66 ^{<i>c</i>}

^{*a*} Conditions: **1b**, **1e–11** (0.5 mmol), **2a** (1 mmol), $Ru(bpy)_3Cl_2$ (0.01 mmol), Et_3N (0.2 mmol), 4-methoxypyridine (0.2 mmol), base (0.5 mmol), DMF (2 mL), irradiation with 23 W household light bulb at about 35 °C for 24 h. ^{*b*} Isolated yields. ^{*c*} dr = 11:1.

Table 3 Scope of secondary and tertiary α -carbonyl alkyl or aryl bromides reaction with $1b^{a}$



^{*a*} Conditions: **1b** (0.5 mmol), **2m–2r** (1 mmol), $\operatorname{Ru}(\operatorname{bpy})_3\operatorname{Cl}_2$ (0.01 mmol), $\operatorname{Et}_3\operatorname{N}$ (0.2 mmol), 4-methoxypyridine (0.2 mmol), base (0.5 mmol), DMF (2 mL), irradiation with 23 W household light bulb at 35 °C for 24 h. ^{*b*} Isolated yields.

were obtained (Table 3). Substrates bearing more than one substituent at the α -position of α -brominated carboxylates and ethyl bromoacetate resulted in relatively poor yields (**3n**-**3p**) with the formation of acetophenone, which results from the hydrolysis of enamine. When cinnamyl or allyl α -brominated carboxylates were employed as substrates, moderate yields were obtained without an intramolecular cyclization product.

Control experiments were conducted to ensure whether the reaction occurred *via* a radical addition reaction irradiated by visible light or by a direct substitution reaction under thermal conditions. We conducted the reaction in dark under different temperatures, ranging from 40 $^{\circ}$ C to 100 $^{\circ}$ C, and only small amounts of desired products were isolated. Meanwhile, we ruled out the radical-chain propagation mechanism based on the experiments of turn-on/turn-off the light (see ESI†).

On the basis of the aforementioned experiments, a plausible mechanism for the reaction is shown in Scheme 4. The excitation



Scheme 4 Proposed mechanism.

of the metal catalyst under visible light generates the excited $[Ru(bpy)_3]^{2+*}$ species, ¹⁴ which oxidizes Et₃N to give the active single electron transfer species, $[Ru(bpy)_3]^+$, along with the radical cation of the amine. Then, the electron-rich metal complex $[Ru(bpy)_3]^+$ reduces the activated C–Br bond^{1*m*,10} to furnish the electron-deficient radical I and regenerates $[Ru(bpy)_3]^{2+}$. The rapid addition of radical I to the electron-rich enamine forms radical II, which can be rapidly oxidized to iminium cation **2** and undergoes single-electron transfer to give $[Ru(bpy)_3]^{2+*}$,³ and forms the metal complex $[Ru(bpy)_3]^+$ to complete the photoredox catalytic cycle. Finally, the γ -keto ester **3** can be obtained by the hydrolysis of the iminium cation **2**.¹⁵

In summary, we developed an efficient visible-lightmediated photoredox reaction of α -brominated carboxylates with enamines *via* an intermolecular radical addition reaction. This method provided a novel access to various synthetically important γ -ketoesters in good yields under very mild conditions. Further work toward expanding the use of photoredox catalysis in the context of radical chemistry is undergoing.

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